17

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number
WO 03/013502 A1

(51) International Patent Classification[7]: A61K 31/25, C07D 309/30

(21) International Application Number: PCT/US02/24932

(22) International Filing Date: 6 August 2002 (06.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/310,555 7 August 2001 (07.08.2001) US

(71) Applicant (*for all designated States except US*): **THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA** [US/US]; 3160 Chestnut Street, Suite 200, Philadelphia, PA 19104-6283 (US).

(72) **Inventors; and**
(75) **Inventors/Applicants** (*for US only*): **SMITH, Amos, B., III** [US/US]; 517 General Lafayette Road, Merion, PA 19066 (US). **BEAUCHAMP, Thomas, J.** [US/US]; 7277 Leawood Street, Portage, MI 49024-4079 (US). **LAMARCHE, Matthew, J.** [US/US]; 2300 Pine Street, Apt. 12, Philadelphia, PA 19103 (US). **RUCKER, Paul** [US/US]; 99 East Glenolden Avenue, A-311, Glenolden, PA 19036 (US).

(74) **Agents: DELUCA, Mark** et al.; Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia, PA 19103 (US).

(81) **Designated States** (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/013502 A1

(54) **Title:** COMPOUNDS WHICH MIMIC THE CHEMICAL AND BIOLOGICAL PROPERTIES OF DISCODERMOLIDE

(57) **Abstract:** Compounds which mimic the chemical and/or biological activity of discodermolide are provided.

COMPOUNDS WHICH MIMIC THE CHEMICAL AND BIOLOGICAL PROPERTIES OF DISCODERMOLIDE

GOVERNMENT SUPPORT

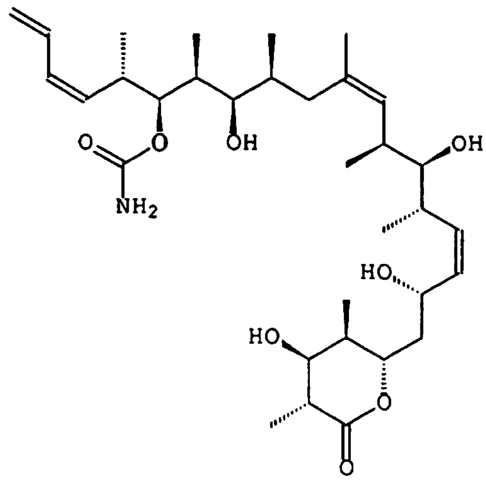
Certain of the inventors were supported by National Institutes of Health Grant GM-29028.

FIELD OF THE INVENTION

This invention relates to compounds which mimic the chemical and/or biological activity of discodermolide, and to methods and intermediates useful in their preparation.

BACKGROUND OF THE INVENTION

In 1990, Gunasekera and co-workers at the Harbor Branch Oceanographic Institute reported the isolation of (+)-discodermolide (**1**), an architecturally novel metabolite of the marine sponge *Discodermia dissoluta* (0.002% w/w). (*See*, Gunasekera, *et al.*, *J. Org. Chem.* **1990**, *55*, 4912. Correction: *J. Org. Chem.* **1991**, *56*, 1346).



(+)-1

Initial studies revealed that (+)-discodermolide suppresses both the two-way mixed-lymphocyte reaction and the concanavalin A-induced mitogenesis of murine splenocytes in vitro with no associated cytotoxicity. Moreover, (+)-**1** suppresses the *in vivo* graft-vs.-host splenomegaly response induced by injection of parental splenocytes into F1 recipient mice, with potency intermediate between those of cyclosporin A and FK506. (Longley, *et al.*, *Transplantation* **1991**, *52*, 650; Longley, *et al.*, *Transplantation* **1991**, *52*, 656; Longley, *et al. Ann. N.Y. Acad. Sci.* **1993**, *696*, 94). These findings stimulated the recent discovery that (+)-**1** arrests cell development at the M phase by binding and stabilizing mitotic spindle microtubules; thus discodermolide resembles taxol in its mode of action, but the microtubule binding affinity of **1** is much higher. (ter Haar, *et al.*, *Biochemistry* **1996**, *35*, 243; Hung, *et al.*, *Chemi.& Biol.* **1996**, *3*, 287). These and other results suggest that (+)-discodermolide holds considerable promise as an anticancer agent. The scarcity of natural material however has precluded a complete evaluation of its biological profile.

The absolute configuration of discodermolide

remained undefined until Schreiber et al. synthesized both antipodes of **1**. (Nerenberg, *et al. J. Am. Chem. Soc.* **1993**, *115*, 12621; Hung, *et al.*, *Chem. & Biol.* **1994**, *1*, 67). Interestingly, the unnatural (-) antipode also displays significant immunosuppressant activity. Recently, the solution structure of (+)-Discodermolide has been reported as well as its conformation in DMSO. Smith, et al., "Solution Structure of (+)-Discodermolide", *Organic Letters*, **2001**, Vol. 3, No. 5, 695-698 and Montcagudo et al., "The Conformation of Discodermolide in DMSO", *J. Am. Chem. Soc.*, **2001**, 123(28), 6929-6930.

Microtubules are believed to be required for a host of normal cellular processes, most importantly mitosis and cell division. When such a structure and its related biological functions are disrupted, cells can no longer undergo a normal cell cycle and eventually will die. Accordingly, microtubules have become a key target for cancer chemotherapeutic drugs with many diverse natural compounds targeting the tubulin/microtubule system.

Taxol, isolated from the Pacific Yew tree, has activity against a variety of human carcinoma cell lines and has been approved for the treatment of human breast, ovarian, and lung carcinomas. Rowinsky, E.K, "The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents," *Annu. Rev, Med.* **1997**, 48, 353-374. *In vitro*, Taxol induces microtubule assembly in the absence of GTP that is normally required for assembly. Schiff, P.B., et al., "Promotion of microtubule assembly *in vitro* by Taxol," *Nature* (Lond.) **1979**, 277, 665-667. The resultant microtubules are stable against depolymerizing conditions such as cold temperatures or the addition of Ca^{2+}. Thus, Taxol blocks cells in the mitotic phase of the cell cycle and causes microtubule bundling, ultimately leading to cell death. Schiff, P.B., et al., "Taxol stabilizes microtubules in mouse fibroblast cells", *Proc. Natl. Acad. Sci.* USA,**1980**,

77, 1561-1565; Jordan, M.A., et al., "Mitotic block induced in HeLa cells by low concentrations of paclitaxel (Taxol) results in abnormal mitotic exit and apoptotic cell death", *Cancer Res*. **1996**, 56, 816-825; Torres, K., et al., "Mechanisms of Taxol-induced cell death are concentration dependent", *Cancer Res.*, **1998**, 58, 3620-3626. Even at low concentrations, the drug has a major effect on the dynamic instability of microtubules, reducing the dynamics dramatically. Jordan, M.A., et al., "Mechanism of mitotic block and inhibition of cell proliferation by Taxol at low concentrations", *Proc. Natl. Acad. Sci. USA*, **1990**, 90, 9552-9556; Derry, W.B., et al., "Substoichiometric binding of Taxol suppresses microtubule dynamics", *Biochemistry*, **1995**, 34, 2203-2211.

Other novel tubulin-stabilizing agents, such as the epothilones, eleutherobin, and (+)-discodermolide, have been identified. Bollag, D.M., et al., "Epothilones, a new class of microtubule-stabilizing agents with a Taxol-like mechanism of action", *Cancer -Res.*, **1995**, 55, 2325-2333; Lindel, T., et al., "Eleutherobin, a new cytotoxin that mimics Paclitaxel (Taxol) by stabilizing microtubules", *J. Am. Chem. Soc.*, **1997**, 119, 8744-8745; Ter Haar, et al., "Discodermolide, a cytotoxic marine agent that stabilizes microtubles more potently than Taxol", *Biochemistry*, **1996**, 35 243-250; Hung, D.T., et al., "(+)-Discodermolide binds to microtubules in stoichiometric ratio to tubulin dimers, blocks taxol binding and results in mitotic arrest", *Chem. Biol.*, **1996**, 3, 287-293. These natural products have been isolated from a *Myxobacterium* fermentation, a marine soft coral, and a marine sponge, respectively. The new compounds appear to have a mechanism of action very similar to that of Taxol in that they promote the assembly of stable microtubules, and induce mitotic arrest and microtubule bundling in cells, although each with a unique potency. A number of structure-activity relationship (SAR) and modeling

studies have been performed with Taxol, the epothilones, eleutherobin, and (+)-discodermolide in a search for a common pharmacophore model for these drugs. Winkler, J.D., et al., "A model for the Taxol (Paclitaxel)/epothilone pharmacophore", *Bioorg. Afed. Chem. Lett.*, **1996**, 6, 2963-2966; Ojima, I., et al., "A common pharmacophore for cytotoxic natural products that stabilize microtubules", *Proc. Nati. Acad. Sci. USA,* **1999**, 96, 4256-4261; Wang, M..,et al., "A unified and quantitative receptor model for the microtubule binding of Paclitaxel and epothilone", *Org. Lett.*, **1999**, 1, 43-46; He, L., et al., "A common pharmacophore for Taxol and the epothilones based on the biological activity of a taxane molecule lacking a C-13 side chain", *Biochemistry*, **2000**, 39, 3972-3978; Giannakakou, P., "A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells", *Proc. Natl. Acad. Sci. USA*, **2000**, 97, 2904-2909.

Although (+)- discodermolide was isolated and originally identified as a potential immunosuppressive agent, further studies revealed that the target of (+)-discodermolide was the microtubule system. Longley, R.E., et al., "Immunosuppression by discodermolide", *Ann. N.Y. Acad Sci.*, **1993**, 696, 94-107; *see*, reports of Ter Haar, et al. and Hung, D.T., et al. noted above. For example, when compared to Taxol, (+)-discoderrnolide was found to be more potent at nucleating tubulin assembly and at inducing microtubule bundles in MCF-7 cells, and to have a higher affinity for tubulin. See report of Ter Harr, et al. noted above and Kowalski, R.J., et al., "The microtuble-stabilizing agent discodermolide competitively inhibits the binding of Paclitaxel (Taxol) to tubulin polymers, enhances tubulin nucleation reactions more potently than Paclitaxel, and inhibits the growth of Paclitaxel-resistant cells", *Mol. Pharmacol.*, **1997**, 52, 613-622. In cells, however, (+)-

discodermolide was less cytotoxic than Taxol. *See* Kowalski et al. noted above and Martello, L.A., et al., "Taxol and discodermolide represent a synergistic drug combination in human carcinoma cell lines", *Clin. Cancer Res.*, **2000**, 6, 1978-1987. Moreover, it has been recently reported that Taxol and (+)-discodermolide represent a synergistic drug combination in human carcinoma cell lines, and as such may comprise a useful chemotherapeutic drug combination. *See* report of Martello noted above.

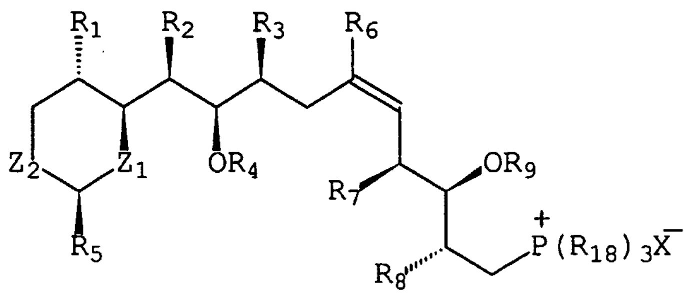
The scarcity of the natural product discodermolide (0.002% w/w from frozen sponge) has effectively precluded further development of this agent as a drug. It is therefore not surprising that discodermolide has attracted considerable interest from the synthetic community resulting in various synthetic approaches. Nerenberg, J.B., et al., "Total synthesis of the immunosuppressive agent (-)-discodermolide", *J Am. Chem. Soc.*, **1993**, 115, 12621-12622; Smith, A.B., III, et al., "Total synthesis of discodermolide", *J Am. Chem. Soc.*, **1995**, 117, 12011-12012; Harried, S.S., et al., "Total synthesis of discodermolide: an application of a chelation-controlled alkylation reaction", *J Org. Chem.*, **1997**, 62, 6098-6099; Marshall, J.A., et al., "Total synthesis of (+)-discodermolide," *J Org. Chem.*, **1998**, 63, 7885-7892; Halstead, D.P., "Total synthesis of (+)-miyakolide, (-)-discodermolide, and discodermolide", PhD thesis, **1998**, pp. 1-199, Harvard University, Cambridge, USA; Smith, A.B., III, et al., "Gram-scale synthesis of (+)-discodermolide", *Org. Lett.*, **1999**, 1, 1823-1826; Paterson, I., et al., "Total synthesis of the antimicrotuble agent (+)-discomoderlide using boron-mediated aldol reactions of chiral ketones", *Angew. Chem. Int. Ed.*, **2000**, 39, 377-380.

There is, therefore, both a need for improved synthetic methods for the preparation of discodermolide and compounds having similar chemical and/or biological activity as discodermolide.

SUMMARY OF THE INVENTION

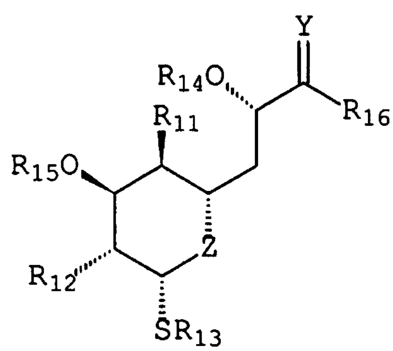
A class of compounds has been discovered that stabilize microtubules, a key target for cancer chemotherapeutic drugs. These compounds appear to profoundly enhance the initiation process of microtubule polymerization compared to Taxol® and are expected to find use against Taxol®-resistant cell lines that overexpress P-glycoprotein, the multidrug resistant transporter.

Thus, in one aspect, the present invention provides synthetic methods for the discodermolides and other polyhydroxylactones. In one aspect, such methods include contacting a phosphonium salt of formula I:



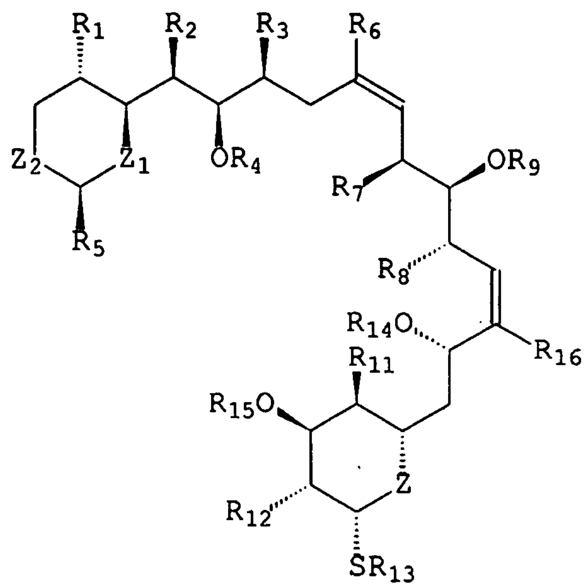
I

with base and an alkylthiol of formula II:



II

to form a diene of formula III:



III

wherein:

R_1, R_2, R_3, R_7, R_8, R_{11}, R_{12} and R_{13} are, independently, C_1-C_{10} alkyl;

R_6 is H or C_1-C_{10} alkyl;

X is a halogen;

Z, Z_1, and Z_2 are, independently, O, S or NR';

R_4, R_9, R_{14}, and R_{15} are, independently, acid labile hydroxyl protecting groups;

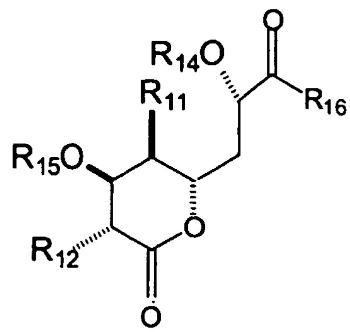
R_5 is C_6-C_{14} aryl;

Y is O, S or NR';

R' and R_{16} are, independently, hydrogen or C_1-C_6 alkyl; and

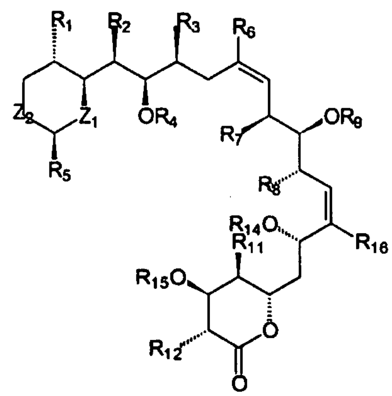
R_{18} is C_6-C_{14} aryl.

In another embodiment, compounds of formula I are contacted with compounds of the following formula XXIII:



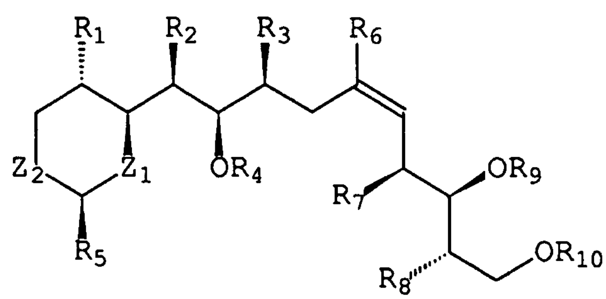
XXIII

to form a diene of formula XXXXX:



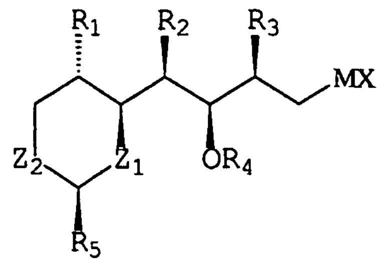
XXXXX

In another aspect, the methods of the invention involve producing an alkene of formula IV.



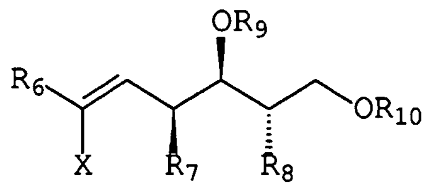
IV

This can be accomplished by contacting an organometallic reagent of formula Va:



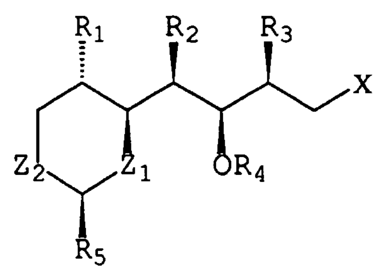
Va

with a vinyl halide of formula VIa:



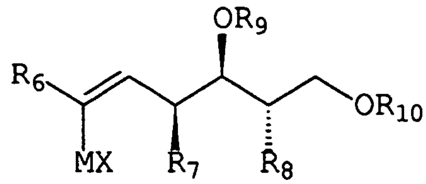
VIa

wherein M is Li, Cu, Mg, or Zn and R_{10} is an acid stable hydroxyl protecting group and all other variables are as defined above. Alternatively, a vinyl halide of formula Vb:



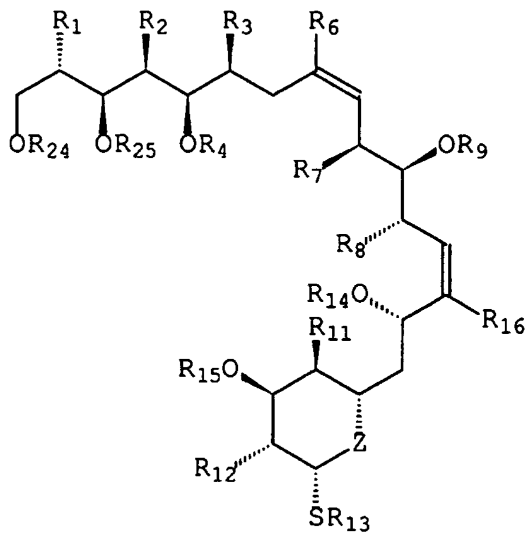
Vb

can be contacted with an organometallic compound of formula VIb:



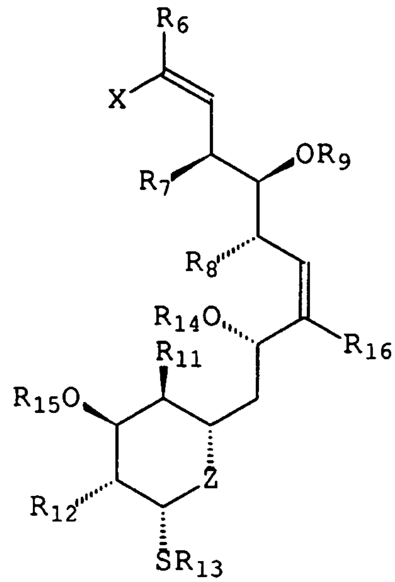
VIb

In yet another aspect, the methods of the invention involve compounds having formula VII.



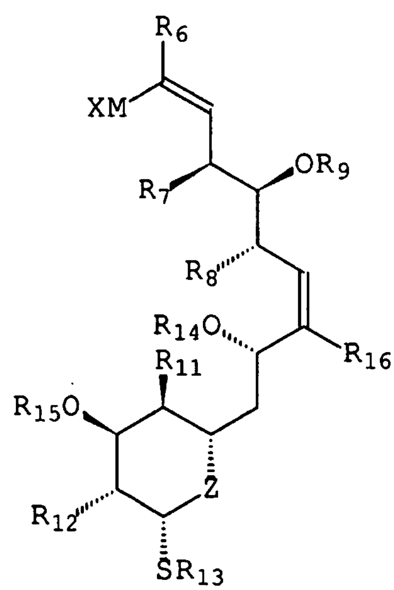
VII

by contacting a diene of formula VIIIa:



VIIIa

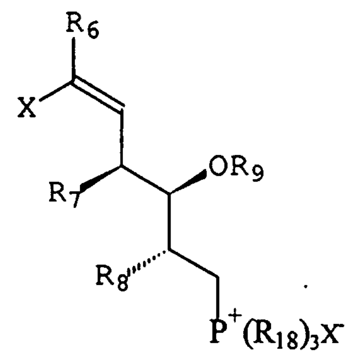
with an organometallic compound having formula Va wherein R_{24} is hydrogen and R_{25} is hydrogen or an acid stable hydroxyl protecting group. Alternatively, an organometallic compound having formula VIIIb can be contacted with a vinyl halide having formula Vb.



VIIIb

The methods of the invention also involve producing dienes having formula VIIIa by contacting

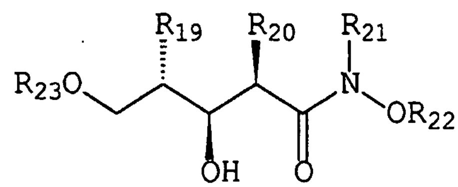
phosphonium salts having formula IX:



IX

with base and alkylthiol compounds having formula II.

The present invention also provides synthetic intermediates which are useful in the preparation of polyhydroxylactones, including the compounds having formulas I-IX and X:



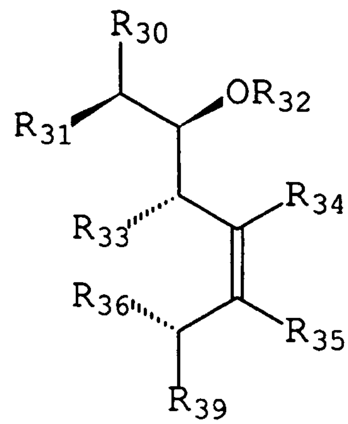
X

wherein:

R_{19}, R_{20}, R_{21} and R_{22} are, independently, C_1-C_{10} alkyl; and

R_{23} is C_7-C_{15} aralkyl.

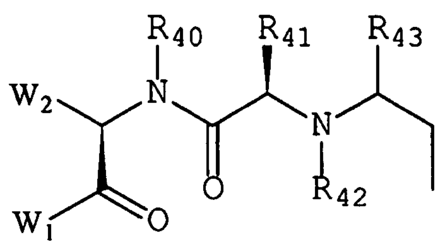
The present invention also provides compounds which mimic the chemical and/or biological activity of the discodermolides. In preferred embodiments, such compounds have formula XI:



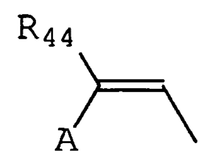
XI

where

R_{30} is substituted or unsubstituted C_1-C_{10} alkyl or a moiety formula XII or XIII:

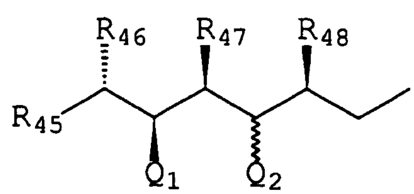


XII



XIII

where A is C_1-C_{20} alkyl, $-CH_2NH(T)$ or a moiety of formula XIV:



XIV

wherein

T is peptide having 1 to about 10 amino acids;

R_{32}, R_{40}, R_{42}, R_{43}, R_{46}, R_{47}, and R_{48} are, independently, hydrogen or C_1-C_6 alkyl;

R_{41} is a side chain of an amino acid;

W_1 and W_2 are, independently, $-OR_{49}$ or $-NHP_1$;

P_1 is hydrogen or an amine protecting group;

R_{33} and R_{36} are, independently, hydrogen, C_1-C_{10} alkyl, $-OR_{50}$, =O or together form $-CH_2-CH_2-$;

R_{34} and R_{35} are, independently, hydrogen or together form -C(H)=C(H)-C(H)=C(H)-;

R_{39} is $-OR_{51}$ or $-CH_2-R_{51}$;

R_{31} and R_{44} are, independently, C_1-C_{10} alkyl;

Q_1 and Q_2 are, independently, hydrogen, $-OR_Q$, $-NHR_{52}$, $-OC(=O)NH_2$ or together form -O-C(O)-NH-;

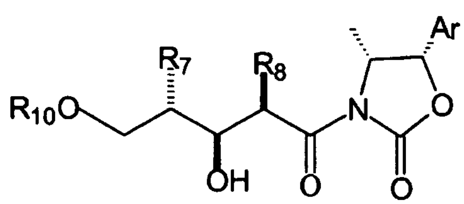
R_Q is hydrogen or a hydroxyl protecting group;

R_{51} is substituted or unsubstituted C_6-C_{14} aryl, tetrahydropyranyl, furanosyl, pyranosyl (*e.g.*, tetramethylfucosyl, tetramethylmannosyl, tetramethylgaractosyl and tetramethylglucosyl), C_3-C_{10} lactonyl or 2-pyranonyl;

R_{45} is C_1-C_6 alkenyl, C_1-C_6 alkyl, C_6-C_{14} aryl, C_2-C_{10} heterocycloalkyl, C_3-C_{10} cycloalkyl, or C_7-C_{15} aralkyl; and

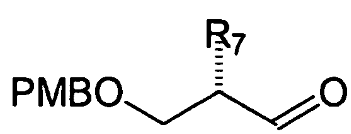
R_{49}, R_{50}, and R_{52} are, independently, hydrogen or C_1-C_6 alkyl.

In another aspect, the present invention provides processes for preparing amides having formula XX:



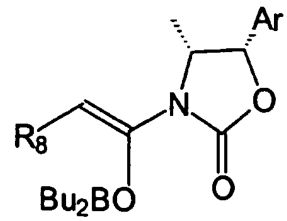
XX

wherein Ar is C_6-C_{14} aryl comprising the steps of contacting a compound having formula XXI:



XXI

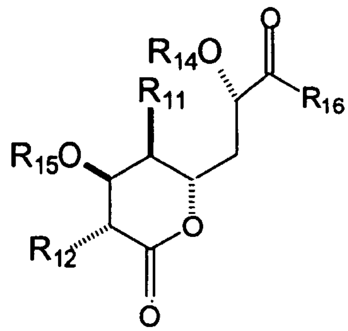
with a compound having formula XXII:



XXII

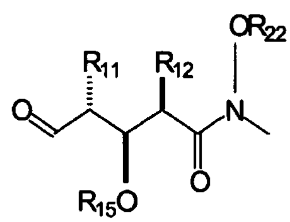
for a time and under conditions effective to form the amide.

Also provided are processes for producing compounds of formula XXIII:



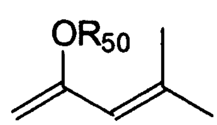
XXIII

comprising the steps of contacting an aldehyde of formula XXIV:

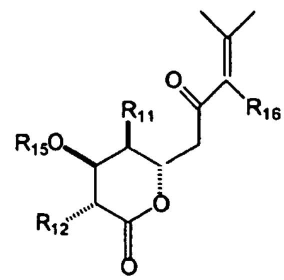


XXIV

with an enol ether of formula XXV:



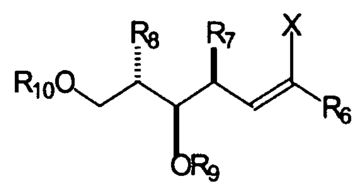
in the presence of a titanium salt for a time and under conditions effective to form an enone of formula XXVI:



XXVI

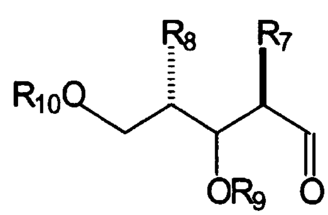
Such enones are then contacted with a reducing agent for a time and under conditions effective to form a corresponding enol, which is contacted with a compound having formula R-L (wherein L is a leaving group) for a time and under conditions effective to form a protected enol. This protected enol is contacted with an oxidizing agent for a time and under conditions effective to oxidize the carbon-carbon double bond of the protected enol.

The invention also provides processes for producing halogenated olefins of formula XXVII:



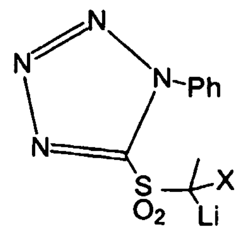
XXVII

by contacting an aldehyde of formula XXVIII:



XXVIII

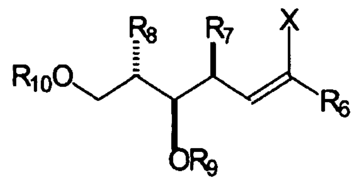
with an α-halo sulfone of formula XXIX:



XXVIX

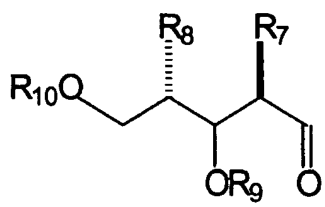
for a time and conditions effective to from the halogenated olefin.

Also provided are processes for producing halogenated olefins of formula XXX:



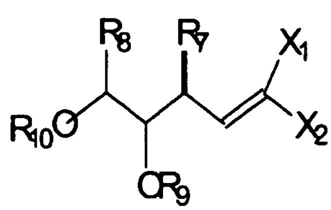
XXX

comprising the steps of contacting a compound of formula XXXI:



XXXI

with triphenylphosphine and a carbon tetrahalide for a time and under conditions effective to form a dihalogenated olefin of formula XXXII:

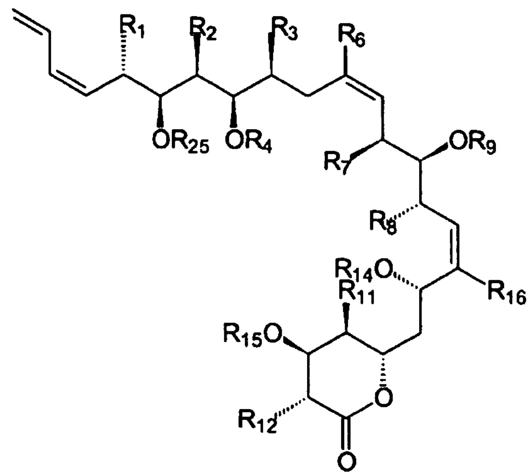


XXXII

Such a dihalogenated olefin is contacted with an organometallic compound (such as lithium dimethyl cuprate or

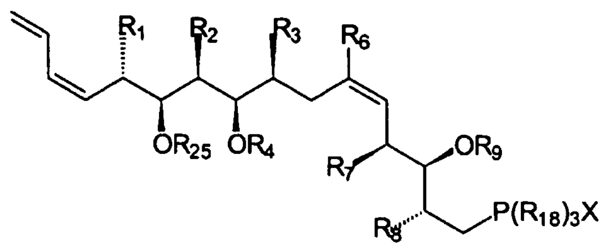
an alkylzinc compound such as methyl zinc chloride or methyl zinc bromide)
in the presence of a catalyst for a time and under conditions effective to form the halogenated olefin.

Additional processes of the invention are directed to synthesis of dienes of formula XXXIII:



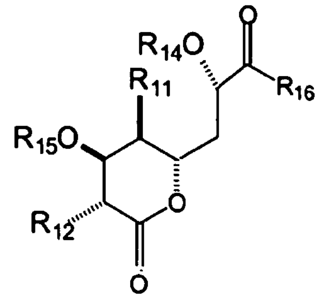
XXXIII

comprising contacting a phosphonium salt of formula XXXIV:



XXXIV

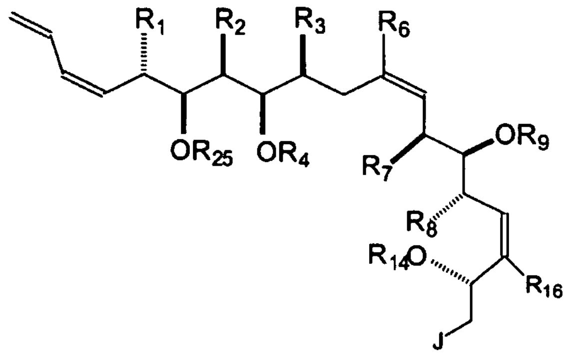
with a base and a compound of formula XXXV:



XXXV

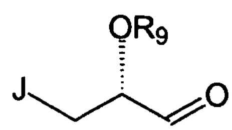
for a time and under conditions effective to form the diene.

The invention also provides processes for producing a compound of formula XXXVI:



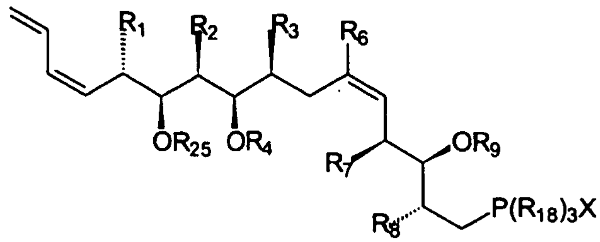
XXXVI

comprising contacting a compound of the formula XXXVII:



XXXVII

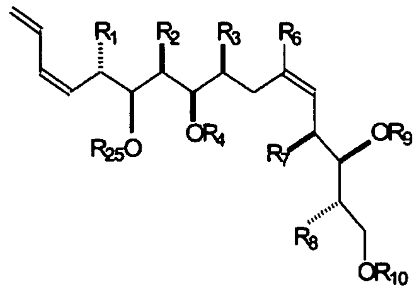
wherein J is C_1-C_{10} alkyl, C_6-C_{14} aryl, C_6-C_{14} alkaryl, C_6-C_{14} alkheteroaryl, C_2-C_{10} heterocycloalkyl. or C_2-C_{10} heterocycloalkenyl (preferably 4-methoxyphenyl, 4-hydroxyphenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl) with a phosphonium salt of formula XXXIV:



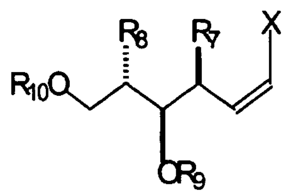
XXXIV

and base.

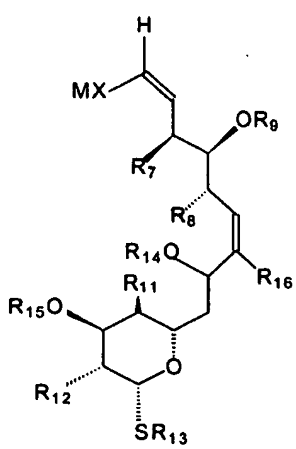
The invention also provides synthetic intermediates having formulas XXXIII-XXXXV:

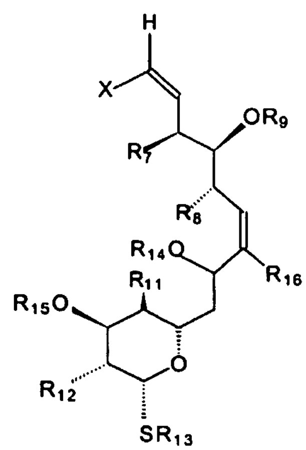


XXXIII

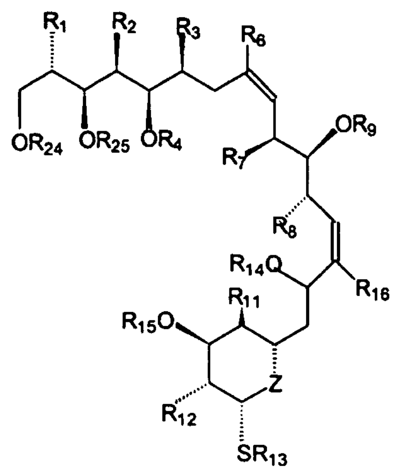


XXXIX

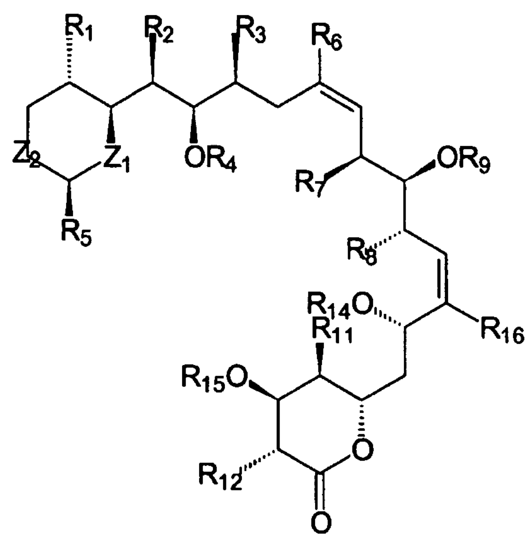




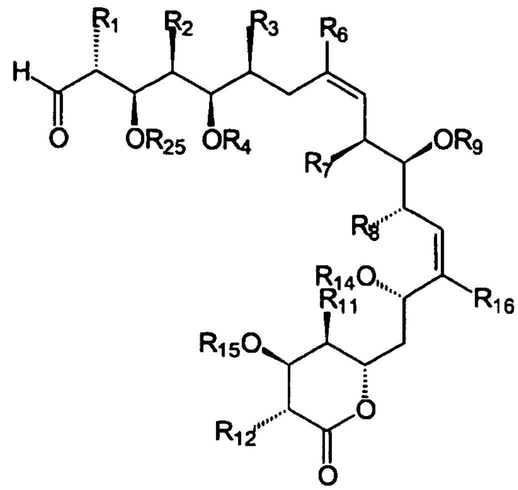
XXXX XXXXI



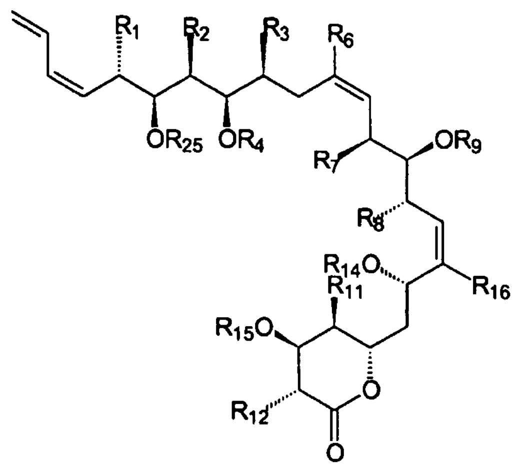
XXXXII



XXXXIII



XXXXIV

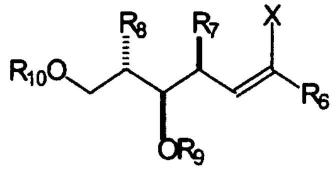


XXXXV

The present invention also provides methods for inhibiting mammalian cell proliferation by contacting mammalian cells with a compound according to the invention or by administering a compound according to the invention (or a pharmaceutical composition comprising such a compound) to a mammal suffering from undesired cell proliferation. Also provided are methods for inhibiting rejection of a transplanted organ in a mammal comprising administering a compound or composition according to the invention to a mammalian organ recipient.

The present invention also provides process for

forming a halogenated olefin of formula:



wherein:

R_6 is selected from H and C_1-C_6 alkyl;

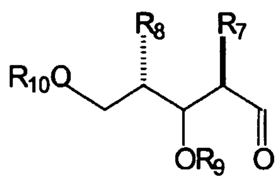
R_7 and R_8 are independently C_1-C_{10} alkyl;

R_9 is an acid labile hydroxyl protecting group;

R_{10} is a protecting group labile to DDQ; and,

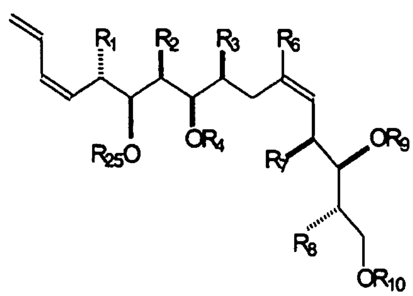
X is halogen;

the process comprising contacting an aldehyde of formula:



with a compound of formula $R_6(R_{18})_3PX$ and X_2 in the presence of base, wherein R_{18} is C_6-C_{14} aryl, for a time and conditions effective to form the halogenated olefin.

The present invention also provides a process for forming a triene of formula:



wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

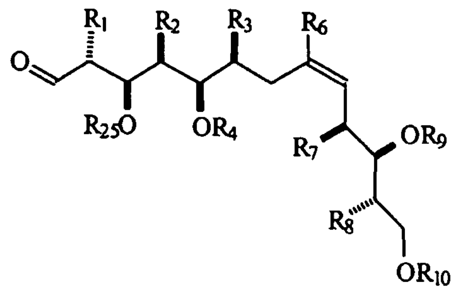
R_3 and R_6 are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are independently acid labile hydroxyl protecting groups;

R_{25} is an acid stable hydroxyl protecting group; and

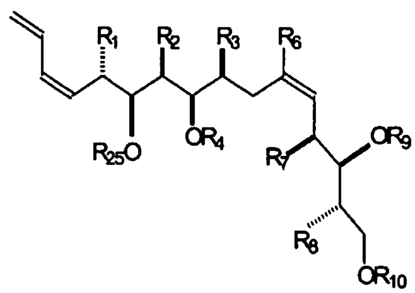
R_{10} is a hydroxyl protecting group;

the process comprising contacting an aldehyde of formula:

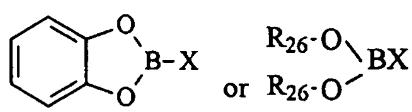


with a compound of formula $Ph_2PCH_2CH=CH_2$ in the presence of a base and a compound of formula $Ti(O-R_{27})_4$, wherein R_{27} is C_{1-6} alkyl; followed by treatment with $R_{28}X$ wherein R_{28} is C_{1-6} alkyl and X is a halogen, for a time and under conditions effective to form the triene.

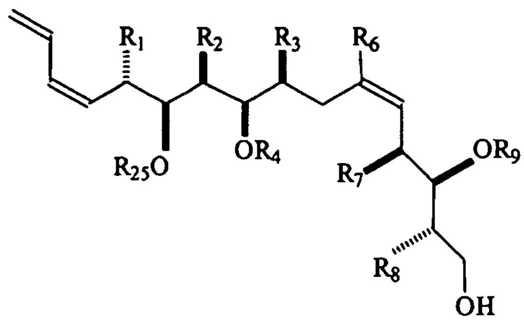
The present invention also provides a process comprising contacting a triene of formula:



with a compound of formula:

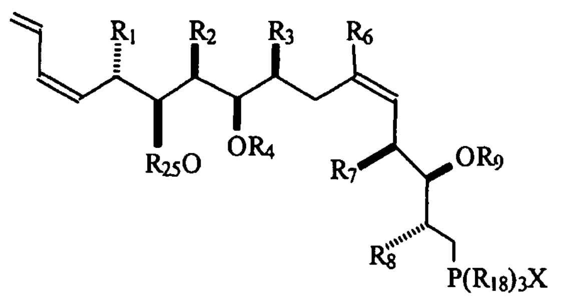


wherein X is a first halogen and R_{26} is selected from C_{6-14} aryl and C_{1-6} alkyl, to form a triene alcohol of formula:

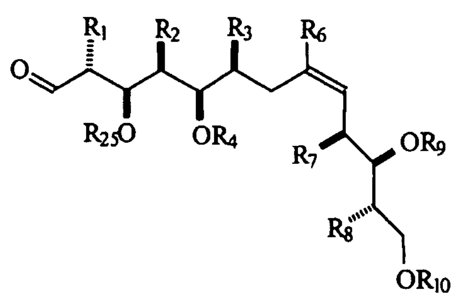


and;

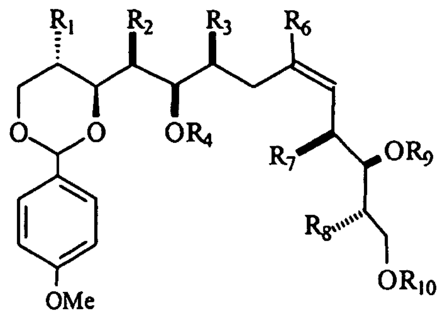
contacting the triene alcohol with Y_2 in the presence of $P(R_{18})_3$ and a base, wherein R_{18} is C_{6-14} aryl and Y is a second halogen, under conditions to form a compound of formula:



The present invention also provides a process of forming an aldehyde of formula:



the process comprising contacting a compound of formula:



wherein:

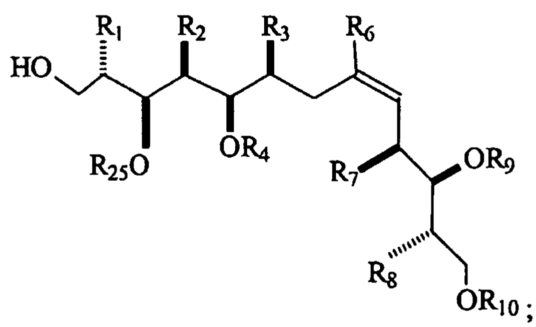
R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

R_3 and R_6 are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are independently acid labile hydroxyl protecting groups; and

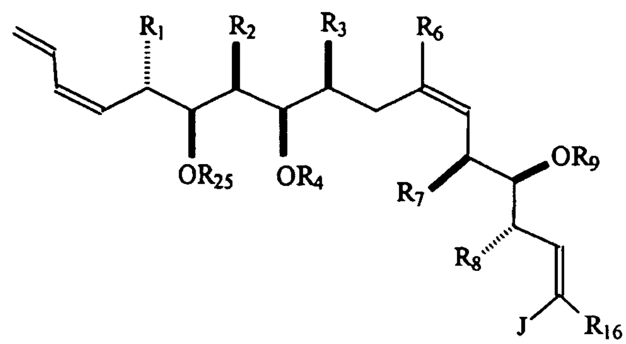
R_{10} is a trityl group;

with hydride to form an alcohol of formula:



and oxidizing the alcohol to form the aldehyde.

The present invention also provides a process for forming a tetraene of formula:



wherein:

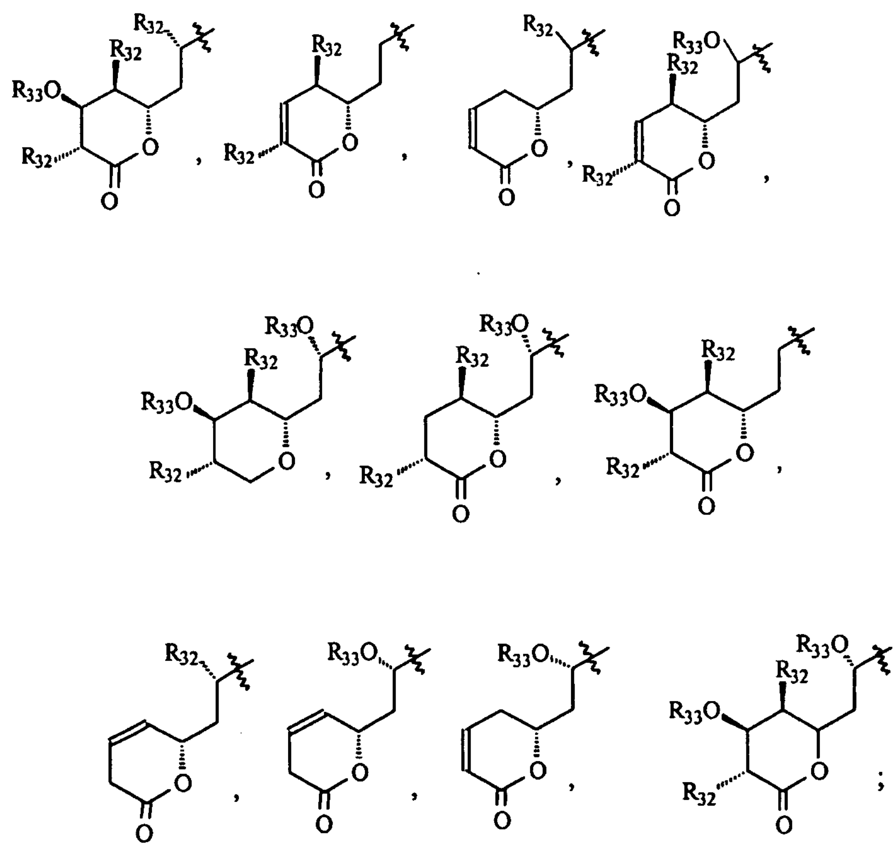
R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

R_3, R_6, and R_{16} are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are independently an acid labile hydroxyl protecting group;

R_{25} is an acid stable hydroxyl protecting group; and

J is selected from:



alkaryl; and alkheteroaryl;

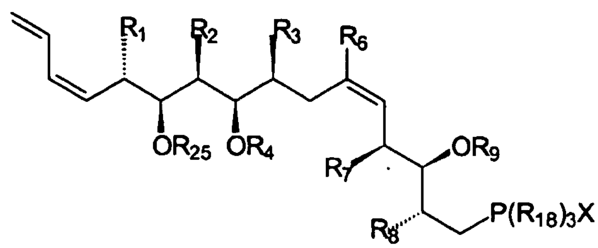
wherein

R_{32} is H or C_1-C_6 alkyl and R_{33} is an acid labile hydroxyl protecting group;

the process comprising contacting a compound of the formula:

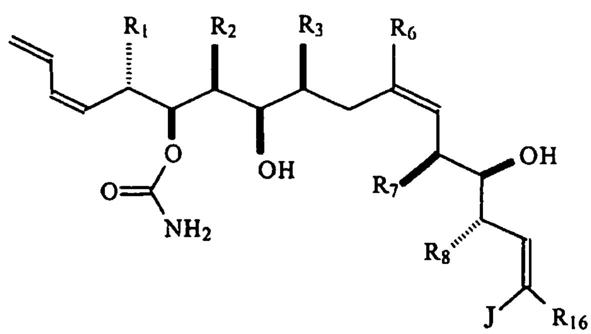
J-CHO

with a phosphonium salt of the formula:



wherein R_{18} is C_6-C_{14} aryl, in the presence of a base for a time and under conditions effective to form the tetraene.

The present invention also provides a process for forming a tetraene of formula:

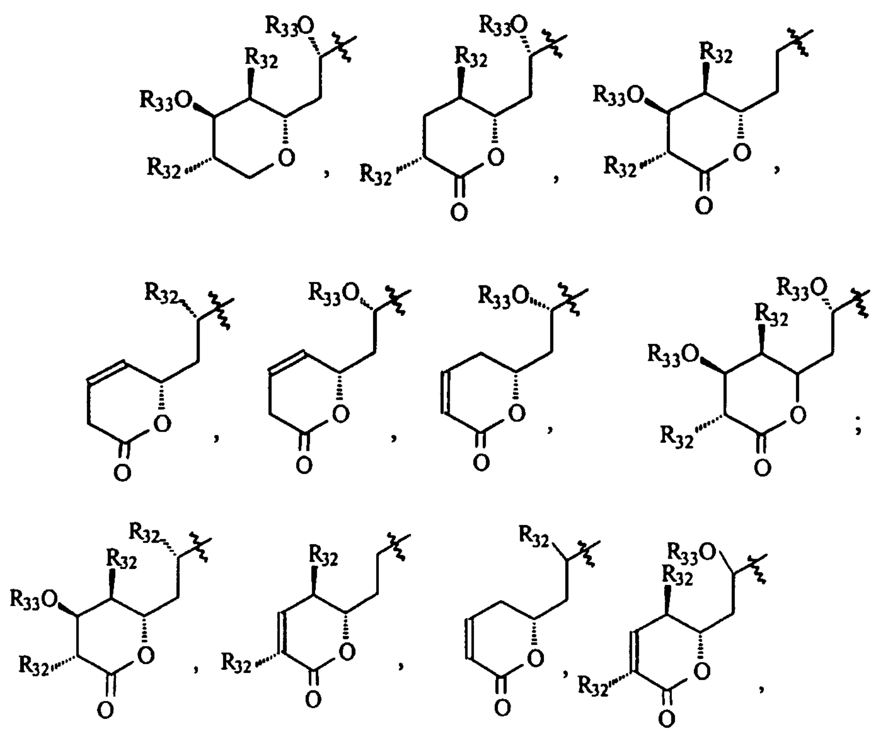


wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

R_3, R_6, and R_{16} are independently selected from hydrogen and C_1-C_6 alkyl; and

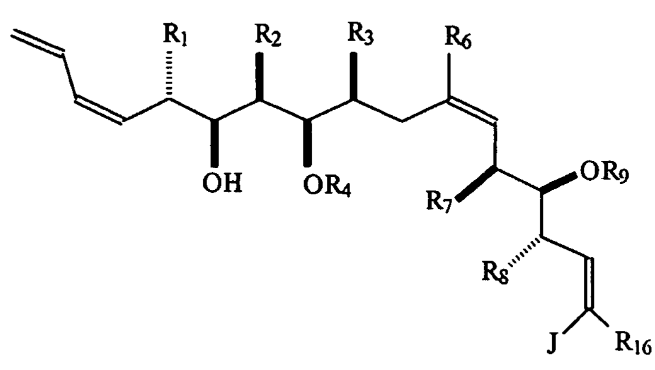
J is selected from:



alkaryl, and alkheteroaryl; wherein

R_{32} is H or C_1-C_6 alkyl and R_{33} is H;

the process comprising contacting an alcohol of formula:

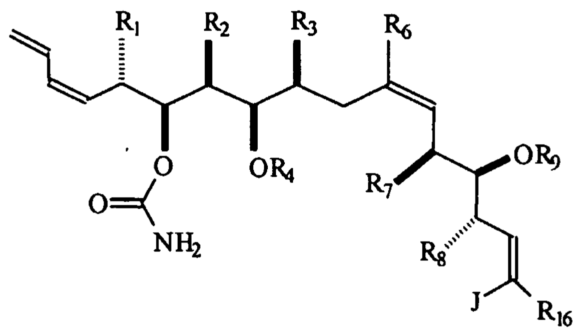


wherein R_4, R_9, and R_{33} are acid labile hydroxyl protecting groups, with an isocyanate of the formula:

$X_3CC(=O)NCO$

wherein X is a halogen, to form a carbamate intermediate;

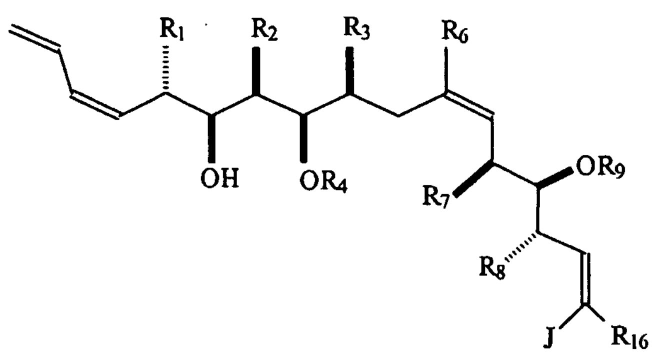
contacting the carbamate intermediate with neutral alumina to form a carbamate of formula:



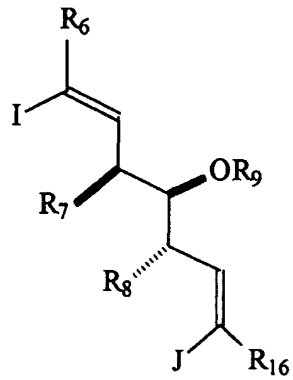
and;

removing the acid labile hydroxyl protecting groups by contacting the carbamate with acid in a protic solvent to form the tetraene.

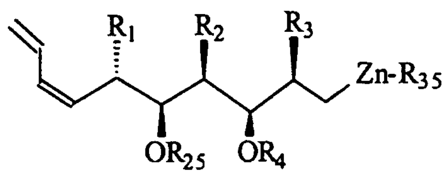
The present invention also provides several processes for forming an alcohol of formula:



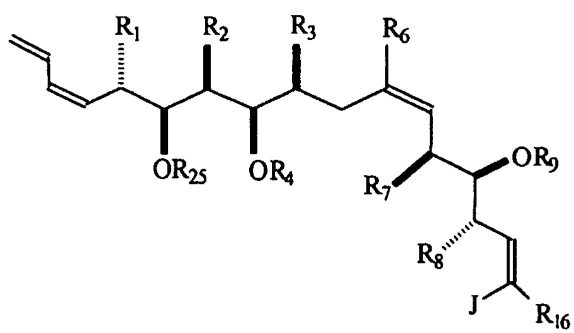
In one process, the process comprises contacting a compound of formula:



with a compound of formula:

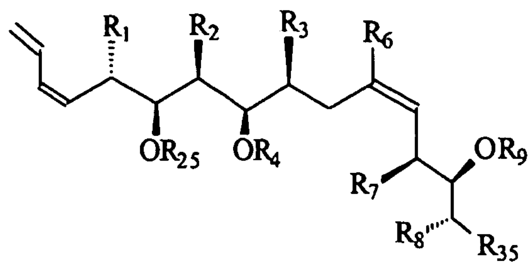


wherein R_{25} is an acid stable protecting hydroxyl protecting group, and R_{35} is selected from C_4 alkyl and a halogen, in the presence of a metal coupling catalyst for a time and under conditions effective to form a coupling product of formula:



and deprotecting the coupling product to form the alcohol.

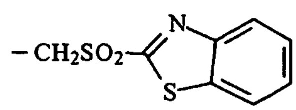
In another process, the alcohol is formed by contacting a compound of formula:



wherein:

R_{25} is an acid stable protecting hydroxyl protecting group;

R_{35} is selected from $CH_2P(R_{18})_3X$, CHO, $-P(=O)Ph_2$, and



;

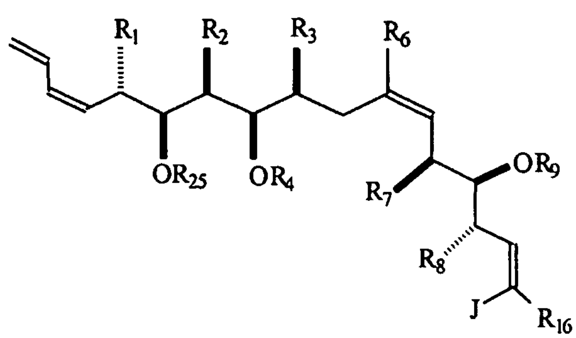
X is a halogen; and

R_{18} is C_{6-14} aryl;

with a compound of formula:

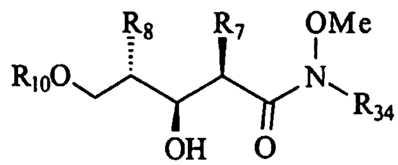
$$J\text{-}R_{35}$$

in the presence of a base to form a coupling product of formula:



and deprotecting the coupling product to form the alcohol.

The present invention also provides a process for forming an alcohol of formula:



wherein:

R_7 and R_8 are independently C_1-C_{10} alkyl;

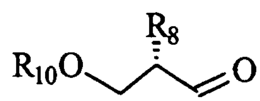
R_{10} is an acid stable hydroxyl protecting group;

R_{34} is selected from $(CH_2)_nC_6$-C_{14} aryl and $(CH_2OCH_2)C_6$-C_{14} aryl, wherein the aryl is substituted with 0-3 R_{35};

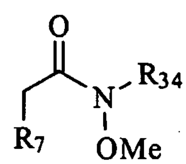
R_{35} is selected from F, CF_3, Br, Cl, and NO_2; and

n is selected from 0 and 1;

the process comprising contacting a compound of formula:

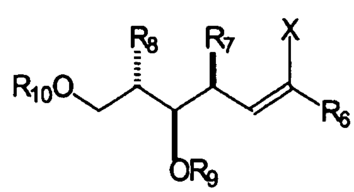


with the enolate of a compound of formula:



in the presence of Lewis acid for a time and under conditions effective to form the alcohol.

The present invention also provides intermediate compounds of formula:



wherein:

R_6 is C_1-C_4 alkyl;

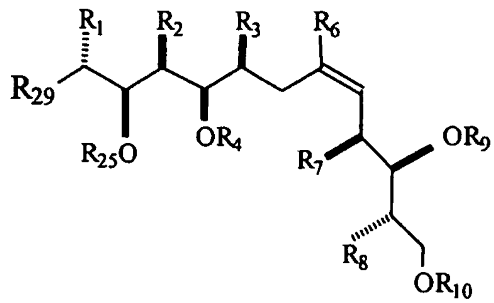
R_7 and R_8 are independently C_1-C_{10} alkyl;

R_9 is an acid labile hydroxyl protecting group;

R_{10} is an acid stable hydroxyl protecting group; and

X is halogen.

The present invention also provides intermediate compounds of formula:



wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

R_3 and R_6 are independently selected from hydrogen and C_1-C_6 alkyl;

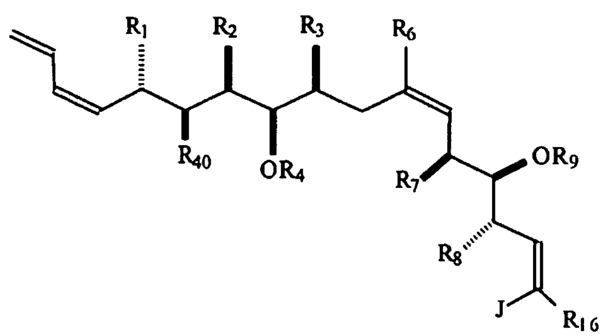
R_4 and R_9 are independently acid labile hydroxyl protecting groups;

R_{25} is an acid stable hydroxyl protecting group; and

R_{10} is a trityl group; and

R_{29} is selected from OH, CHO, and -CH=CH-CH=CH_2.

The present invention also provides a compound of formula:



wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

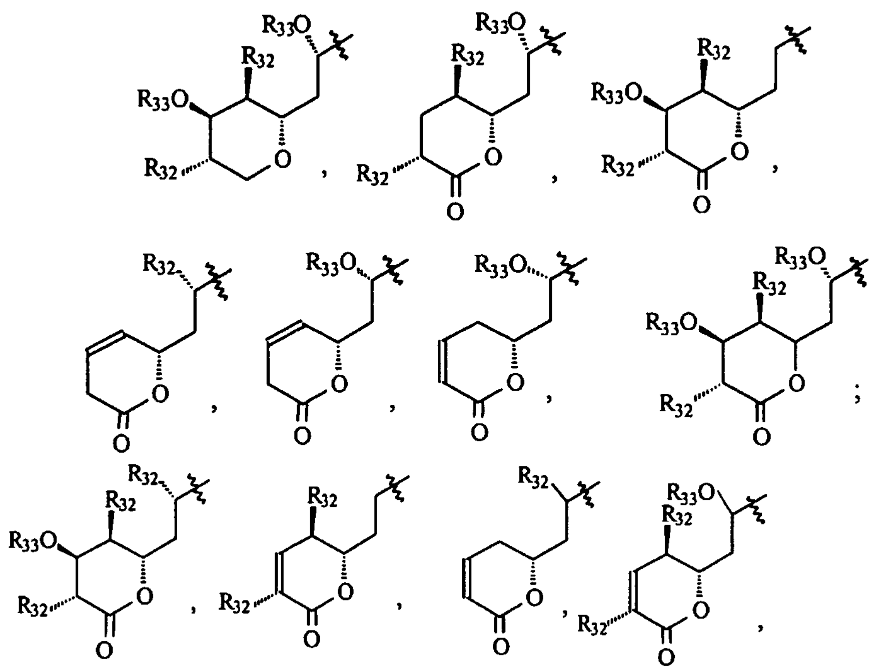
R_3, R_6, and R_{16} are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are acid labile protecting groups;

R_{40} is selected from OR_{25} and $OC(=O)NH_2$;

R_{25} is an acid stable protecting group; and

J is selected from:



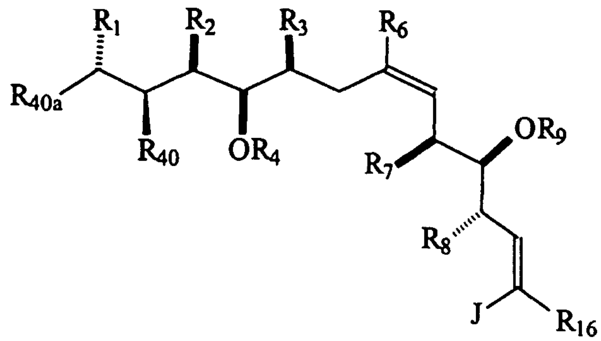
alkaryl and alkheteroaryl;

wherein

R_{32} is C_1-C_6 alkyl; and

R_{33} is selected from H and an acid labile hydroxy protecting group.

The present invention also provides compounds of formula I-a:



I-a

wherein:

R_1, R_2, R_3, R_6, R_7, R_8, and R_{16} are independently selected from hydrogen and C_1-C_{10} alkyl;

R_4 and R_9 are selected from hydrogen and an acid labile protecting group;

R_{40} is $-OC(=R_{25a})NR_{25b}R_{25c}$;

R_{25a} is selected from O, S, NR_{25e};

R_{25e} is selected from hydrogen and C_{1-6} alkyl;

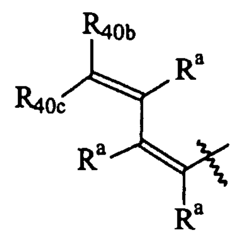
R_{25b} and R_{25c} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, OR^c, $C(=O)R^b$, $S(O)_pR^b$, $(CH_2)_rC_3$-C_{12} carbocycle, and $(CH_2)_r$heterocycle, wherein the alkyl, alkenyl, alkynyl, carbocycle, and heterocycle are substituted with 0-5 R_{25d};

alternatively, R_{25b} and R_{25c} may join with the nitrogen to which they are attached to form a 5- or 6-membered heterocycle containing 0-3 additional heteroatoms selected from O, S, and N, wherein the heterocycle is substituted with 0-5 R_{25d};

R_{25d}, at each occurrence, is selected from F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, OH, NR^aR^a, OR^c, $C(=O)R^b$, CO_2R^c, $OC(=O)R^b$, $NR^aC(=O)R^b$, $C(=O)NR^aR^a$, $OC(=O)NR^aR^a$, $NR^aC(=O)OR^b$, $NR^aS(=O)_2R^b$, $S(=O)_2NR^aR^a$, $NR^aC(=S)R^b$, $C(=S)NR^aR^a$, $NR^aC(=O)NR^aR^a$, $NR^aC(=S)NR^aR^a$, $CH=NOR^c$, $CH=NR^a$, $CH=NNR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $S(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^g$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^g$, C_{1-10} alkyl, C_{2-8}

alkenyl, C_{2-8} alkynyl, phenoxy, benzoyl, C_3-C_{12} carbocycle, and heterocycle, wherein phenoxy, benzoyl, carbocycle and heterocycle are substituted with 0-5 R^e;

R_{40a} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, $(CH_2)_r$heterocycle, wherein R_{40a} is substituted with 0-5 R^e, or alternatively, R_{40a} has the formula:



wherein R_{40b} and R_{40c} are independently selected from hydrogen, F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, $(CH_2)_rNR^aR^a$, $(CH_2)_rOR^c$, $(CH_2)_rC(=O)R^b$, $(CH_2)_rCO_2R^c$, $(CH_2)_rOC(=O)R^b$, $(CH_2)_rNR^aC(=O)R^b$, $(CH_2)_rC(=O)NR^aR^a$, $(CH_2)_rOC(=O)NR^aR^a$, $(CH_2)_rNR^aC(=O)OR^b$, $(CH_2)_rNR^aS(=O)_2R^b$, $(CH_2)_rS(=O)_2NR^aR^a$, $(CH_2)_rNR^aC(=S)R^b$, $(CH_2)_rC(=S)NR^aR^a$, $(CH_2)_rNR^aC(=O)NR^aR^a$, $(CH_2)_rNR^aC(=S)NR^aR^a$, $(CH_2)_rCH{=}NOR^c$, $(CH_2)_rCH{=}NR^a$, $(CH_2)_rCH{=}NNR^aR^a$, $(CH_2)_rC(=NR^a)NR^aR^a$, $(CH_2)_rNR^aC(=NR^a)NR^aR^a$, $(CH_2)_rS(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^9$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^9$, phenoxy, benzoyl, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_3$-C_{10} carbocycle and $(CH_2)_r$heterocycle, wherein alkyl, carbocycle and heterocycle are substituted with 0-5 R^e;

R^a is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, and $(CH_2)_r$heterocycle, wherein R^a is substituted with 0-5 R^e;

R^b is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, and $(CH_2)_r$heterocycle, wherein R^b is substituted with 0-5 R^e;

R^c is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and $(CH_2)_r$phenyl, wherein R^c is substituted with 0-5 R^e;

R^d is independently the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;

R^e is independently selected from F, Cl, Br, I, OR^f, NO_2, CN, CF_3, CF_2CF_3, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, CO_2R^f, $OC(=O)R^f$, $C(=O)R^f$, $NHC(=O)R^f$, $OC(=O)NR^fR^f$, NR^fR^f, $C(=NR^f)NR^fR^f$, $NR^fC(=O)NR^fR^f$, $(CH_2)_r$phenyl, phenoxy, benzoyl, $(CH_2)_r$heterocycle, and =O;

R^f is independently selected from hydrogen and C_{1-6} alkyl;

R^g is independently the residue of an amino acid after the hydrogen of the amine is removed;

J is -A-B or -B;

A is C_{1-6} alkyl substituted with 0-3 R^e;

B is selected from C_3-C_{12} carbocycle and heterocycle wherein carbocycle and heterocycle are substituted with 0-5 R^{Ja};

R^{Ja} is selected from =O, F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, OH, NR^aR^a, OR^c, $C(=O)R^b$, CO_2R^c, $OC(=O)R^b$, $NR^aC(=O)R^b$, $C(=O)NR^aR^a$, $OC(=O)NR^aR^a$, $NR^aC(=O)OR^b$, $NR^aS(=O)_2R^b$, $S(=O)_2NR^aR^a$, $NR^aC(=S)R^b$, $C(=S)NR^aR^a$, $NR^aC(=O)NR^aR^a$, $NR^aC(=S)NR^aR^a$, $CH=NOR^c$, $CH=NR^a$, $CH=NNR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $(CH_2)_rS(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^g$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^g$, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, phenoxy, benzoyl, C_3-C_{12} carbocycle, and heterocycle, wherein phenoxy, benzoyl, carbocycle and heterocycle are substituted with 0-5 R^e;

r is selected from 0, 1, 2, 3, and 4;

q is selected from 1, 2, 3, and 4; and

p is selected from 1 and 2; wherein the compound of formula I-a is other than discodermolide.

BRIEF DESCRIPTION OF THE DRAWINGS

The numerous objects and advantages of the present invention may be better understood by those skilled in the art by reference to the accompanying figures, in which:

Figure 1 shows a retrosynthetic analysis for (-)-discodermolide **1**.

Figure 2 shows a synthetic scheme for compound (+)-**5**.

Figure 3 shows a synthetic scheme for fragment **A**.

Figure 4 shows a synthetic scheme for compound **22**.

Figure 5 shows a synthetic scheme for compound **39**.

Figure 6 shows a synthetic scheme for compounds **15** and **25**.

Figure 7 shows a synthetic scheme for compound **34**.

Figure 8 shows a synthetic scheme for fragment **C**.

Figure 9 shows a synthetic scheme for fragment **B**.

Figure 10 shows a synthetic scheme for compound **39**.

Figure 11 shows a synthetic scheme for compound **40**.

Figure 12 shows a synthetic scheme for compound **49**.

Figure 13 shows a synthetic scheme for compounds **53** and **46**.

Figure 14 shows a synthetic scheme for compound **56**.

Figure 15 shows a synthetic scheme for compound **1**.

Figure 16 shows a synthetic scheme for compound **104**.

Figure 17 shows a synthetic scheme for compound **107**.

Figure 18 shows a synthetic scheme for compound **206**.

Figure 19 shows a synthetic scheme for compound **212**.

Figure 20 shows a synthetic scheme for compound **217**.

Figure 21 shows a synthetic scheme for compound **305**.

Figure 22 shows a synthetic scheme for compound **309**.

Figure 23 shows a synthetic scheme for compound **401**.

Figure 24 shows a synthetic scheme for compound **501**.

Figure 25 shows a synthetic scheme for compound **601**.

Figure 26 shows a synthetic scheme for compound **701** R = alkyl).

Figure 27 shows a synthetic scheme for compound **808**.

Figure 28 shows a synthetic scheme for compound **801**.

Figure 29 shows a synthetic scheme for compound **901**.

Figure 30 shows a synthetic scheme for compound **1003**.

Figure 31 shows a synthetic scheme for compound **1104** (Ar = 2,4-dimethyl-3-methoxyphenyl (a), 2-methyl-5-methoxyphenyl (b), 2,4-dimethyl-5-methoxyphenyl (c), 2,4-dimethylphenyl (d), and 4-methylphenyl (e)).

Figure 32 shows a synthetic scheme for compound **1111**.

Figures 33-36 show representative compounds of the invention.

Figure 37 shows a synthetic scheme for compound **(-)-5**.

Figure 38 shows a synthetic scheme for compound **67**.

Figure 39 shows a synthetic scheme for compound **(+)-B**.

Figure 40 shows a synthetic scheme for compound **58**.

Figure 41 shows a synthetic scheme for compound **86**.

Figure 42 shows a synthetic scheme for compound **58**.

Figure 43 shows a synthetic scheme for compound **(+)-B**.

Figure 44 shows a synthetic scheme for compound **89**.

Figure 45 shows a synthetic scheme for compound **75**.

Figure 46 shows a synthetic scheme for compound **(+)-59**.

Figure 47 shows a synthetic scheme for (+)-discodermolide.

Figure 48 shows a synthetic scheme for compound **95**.

Figure 49 shows a synthetic scheme for compound **94**.

Figure 50 shows a synthetic scheme for compound **58**.

Figure 51 shows a synthetic scheme for compound **1205**.

Figure 52 shows a synthetic scheme for compound **1209**.

Figure 53 shows a synthetic scheme for compound **1211**.

Figure 54 shows a synthetic scheme for compounds **I-i**, **I-ii**, **I-iii**, and **I-iv**.

Figure 55 shows a synthetic scheme for precursor aldehyde **67c**.

Figure 56 shows the structures of (+)-discodermolide, (-)-Taxol®, (-)-Eleutherobin, and (-)-Epothiline A and B.

Figure 57 shows the structures of compounds **I-i, I-ii, I-iii, and I-iv**.

Figure 58 shows a synthetic scheme for compound **75a.**

Figure 59 shows a graph of *in vitro* activities of (-)-Taxol®, (+)-discodermolide, and compounds **I-i, I-ii, I-iii,** and **I-iv** in a tubulin polymerization assay.

Figure 60 shows a graph of results obtained for (+)-discodermolide and compounds **I-i**, **I-ii**, **I-iii**, and **I-iv** in an assay measuring the competitive inhibition of binding of [^{3}H]Taxol to microtubules.

Figure 61 shows the induction of mitotic arrest in A549 cells by (+)-discodermolide and compounds **I-i, I-ii, I-iii,** and **I-iv** as evidenced by flow cytometry analysis.

Figure 62 shows (+)-Discodermolide mimics Taxol and binds into a pocket formed by Gly368, Thr274, His227 and Asp224 in P-tubulin. (a) Model I: the folded U-shaped backbone of (+)-discodermolide matches with the taxane ring of Taxol and the C19 side chain of (+)-discodermolide mimics the C2 side chain of Taxol, while the 8-lactone of (+)-discodermolide emulates the C 13 side chain of Taxol (b) Model II: the 6-lactone of (+)-discodermolide matches with the C2 side chain of Taxol and the C 19 side chain of (+)-discodennolide mimics the C 13 side chain of Taxol. (c) Model I: (+)-Taxotere; (+)-discodermolide (d) Model II: (+)-discodermolide, in the second orientation as seen in (b), fit into the Taxol binding pocket within P-tubulin.

Figure 63 shows a triply convergent synthetic scheme to discodermolide.

Figure 64 shows a synthetic scheme for compound **97a.**

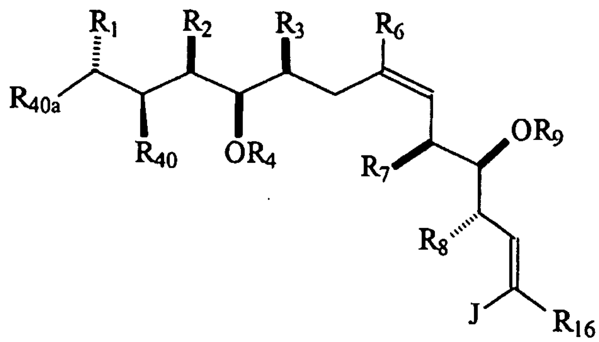
Figure 65 shows a shows a triply convergent synthetic scheme to discodermolide.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one embodiment, the present invention provides compounds that mimic discodermolide. In certain

embodiments, these compounds stabilize microtubules, are active in Taxol-resistant cell lines that overexpress P-glycoprotein, and/or demonstrate an enhancement of the initiation process of microtubule polymerization compared to Taxol.

In certain embodiments, the compounds of the invention have formula I-a:



I-a

wherein:

R_1, R_2, R_3, R_6, R_7, R_8, and R_{16} are independently selected from hydrogen and C_1-C_{10} alkyl;

R_4 and R_9 are selected from hydrogen and an acid labile protecting group;

R_{40} is $-OC(=R_{25a})NR_{25b}R_{25c}$;

R_{25a} is selected from O, S, NR_{25e};

R_{25e} is selected from hydrogen and C_{1-6} alkyl;

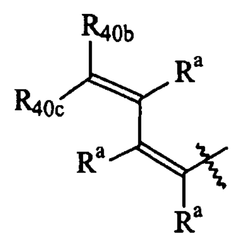
R_{25b} and R_{25c} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, OR^c, $C(=O)R^b$, $S(O)_pR^b$, $(CH_2)_rC_3$-C_{12} carbocycle, and $(CH_2)_r$heterocycle, wherein the alkyl, alkenyl, alkynyl, carbocycle, and heterocycle are substituted with 0-5 R_{25d};

alternatively, R_{25b} and R_{25c} may join with the nitrogen to which they are attached to form a 5- or 6-membered heterocycle containing 0-3 additional heteroatoms selected from O, S, and N, wherein the heterocycle is

substituted with 0-5 R_{25d};

R_{25d}, at each occurrence, is selected from F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, OH, NR^aR^a, OR^c, $C(=O)R^b$, CO_2R^c, $OC(=O)R^b$, $NR^aC(=O)R^b$, $C(=O)NR^aR^a$, $OC(=O)NR^aR^a$, $NR^aC(=O)OR^b$, $NR^aS(=O)_2R^b$, $S(=O)_2NR^aR^a$, $NR^aC(=S)R^b$, $C(=S)NR^aR^a$, $NR^aC(=O)NR^aR^a$, $NR^aC(=S)NR^aR^a$, $CH=NOR^c$, $CH=NR^a$, $CH=NNR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $S(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^g$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^g$, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, phenoxy, benzoyl, C_3-C_{12} carbocycle, and heterocycle, wherein phenoxy, benzoyl, carbocycle and heterocycle are substituted with 0-5 R^e;

R_{40a} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, $(CH_2)_r$heterocycle, wherein R_{40a} is substituted with 0-5 R^e, or alternatively, R_{40a} has the formula:



wherein R_{40b} and R_{40c} are independently selected from hydrogen, F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, $(CH_2)_rNR^aR^a$, $(CH_2)_rOR^c$, $(CH_2)_rC(=O)R^b$, $(CH_2)_rCO_2R^c$, $(CH_2)_rOC(=O)R^b$, $(CH_2)_rNR^aC(=O)R^b$, $(CH_2)_rC(=O)NR^aR^a$, $(CH_2)_rOC(=O)NR^aR^a$, $(CH_2)_rNR^aC(=O)OR^b$, $(CH_2)_rNR^aS(=O)_2R^b$, $(CH_2)_rS(=O)_2NR^aR^a$, $(CH_2)_rNR^aC(=S)R^b$, $(CH_2)_rC(=S)NR^aR^a$, $(CH_2)_rNR^aC(=O)NR^aR^a$, $(CH_2)_rNR^aC(=S)NR^aR^a$, $(CH_2)_rCH=NOR^c$, $(CH_2)_rCH=NR^a$, $(CH_2)_rCH=NNR^aR^a$, $(CH_2)_rC(=NR^a)NR^aR^a$, $(CH_2)_rNR^aC(=NR^a)NR^aR^a$, $(CH_2)_rS(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^g$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^g$, phenoxy, benzoyl, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_3$-C_{10} carbocycle and $(CH_2)_r$heterocycle, wherein alkyl, carbocycle and heterocycle are substituted with 0-5 R^e;

R^a is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl,

$(CH_2)_r$phenyl, and $(CH_2)_r$heterocycle, wherein R^a is substituted with 0-5 R^e;

R^b is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, and $(CH_2)_r$heterocycle, wherein R^b is substituted with 0-5 R^e;

R^c is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and $(CH_2)_r$phenyl, wherein R^c is substituted with 0-5 R^e;

R^d is independently the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;

R^e is independently selected from F, Cl, Br, I, OR^f, NO_2, CN, CF_3, CF_2CF_3, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, CO_2R^f, $OC(=O)R^f$, $C(=O)R^f$, $NHC(=O)R^f$, $OC(=O)NR^fR^f$, NR^fR^f, $C(=NR^f)NR^fR^f$, $NR^fC(=O)NR^fR^f$, $(CH_2)_r$phenyl, phenoxy, benzoyl, $(CH_2)_r$heterocycle, and =O;

R^f is independently selected from hydrogen and C_{1-6} alkyl;

R^g is independently the residue of an amino acid after the hydrogen of the amine is removed;

J is -A-B or -B;

A is C_{1-6} alkyl substituted with 0-3 R^e;

B is selected from C_3-C_{12} carbocycle and heterocycle wherein carbocycle and heterocycle are substituted with 0-5 R^{Ja};

R^{Ja} is selected from =O, F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, OH, NR^aR^a, OR^c, $C(=O)R^b$, CO_2R^c, $OC(=O)R^b$, $NR^aC(=O)R^b$, $C(=O)NR^aR^a$, $OC(=O)NR^aR^a$, $NR^aC(=O)OR^b$, $NR^aS(=O)_2R^b$, $S(=O)_2NR^aR^a$, $NR^aC(=S)R^b$, $C(=S)NR^aR^a$, $NR^aC(=O)NR^aR^a$, $NR^aC(=S)NR^aR^a$, $CH=NOR^c$, $CH=NR^a$, $CH=NNR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $(CH_2)_rS(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^g$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^g$, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, phenoxy, benzoyl, C_3-C_{12} carbocycle, and heterocycle, wherein phenoxy, benzoyl, carbocycle and heterocycle are substituted with 0-5 R^e;

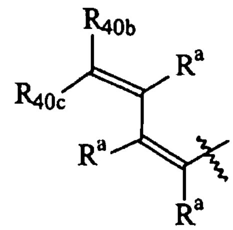
r is selected from 0, 1, 2, 3, and 4;

q is selected from 1, 2, 3, and 4; and

p is selected from 1 and 2; wherein the compound of

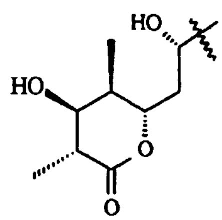
formula I-a is other than discodermolide.

In certain preferred embodiments, when R_1, R_2, R_6, R_7, and R_8 are methyl, R_3 is methyl or hydrogen, R_{25a} is oxygen, and R_4, R_9, R_{16}, R_{25b}, R_{25c} are hydrogen, R^{40a} is

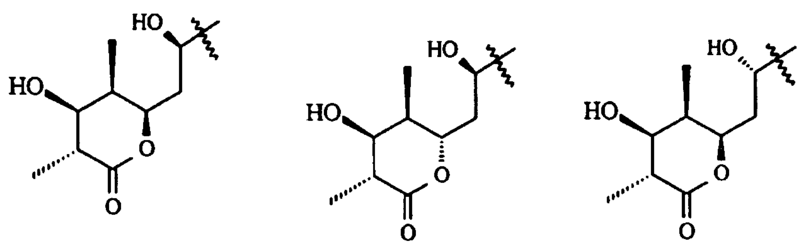


wherein R_{40b} and R_{40c} are hydrogen or one of R_{40b} and R_{40c} is hydrogen and the other is $(CH_2)_3OCOC(CH_3)_3$,

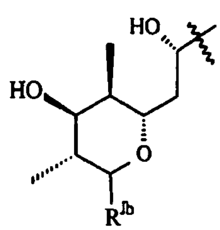
J is other than:



substituted with 0-2 $C(=O)CH_3$;



and



wherein R^{Jb} is S-phenyl or $O(CH_2)_2NHCOalkyl$.

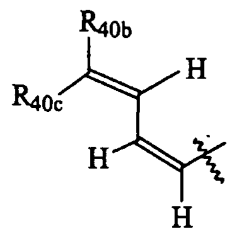
In certain preferred embodiments, R_1, R_2, R_3, R_6, R_7, R_8, and R_{16} are independently selected from hydrogen and methyl;

R_{40} is $-OC(=O)NR_{25b}R_{25c}$;

R_{25b} and R_{25c} are independently selected from hydrogen, $S(O)_2R^b$, C_{1-6} alkyl, $(CH_2)_rC_3$-C_{12} carbocycle, and $(CH_2)_r$heterocycle, wherein alkyl, carbocycle, and heterocycle are substituted with 0-3 R_{25d};

alternatively, R_{25b} and R_{25c} may join with the nitrogen to which they are attached to form a five or six membered heterocycle containing 0-1 additional heteroatom selected from O, S, and N, wherein the heterocycle is optionally substituted with 0-3 R_{25d};

R_{40a} is



A is absent or C_{1-3} alkyl substituted with 0-3 R^e;

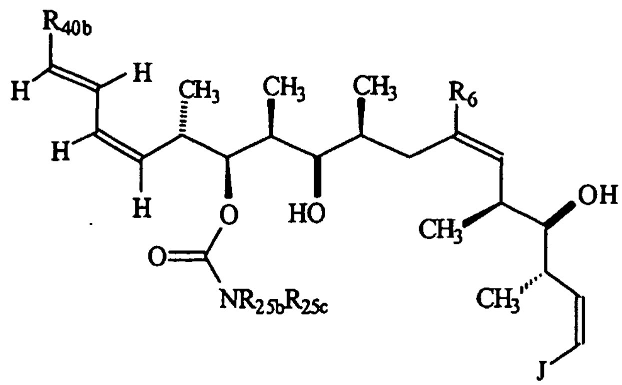
B is selected from C_3-C_6 carbocycle and a 5- or 6-membered heterocycle wherein carbocycle and heterocycle are substituted with 0-5 R^{Ja};

r is selected from 0, 1, 2, and 3; and

q is selected from 1, 2, and 3.

In certain more preferred embodiments, R_3 is methyl.

In certain preferred embodiments, the compounds of the present invention have the formula I-b:



I-b

wherein R^{40b}, R^{25b}, R^{25c}, and J are selected from the above substituents and R^6 is selected from hydrogen and methyl.

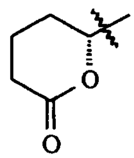
In certain preferred embodiments of the compound of formula I-b, A is absent or selected from CH_2 and CH_2CH_2, wherein the CH_2 and CH_2CH_2 are substituted with 0-1 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, and =O; and

B is selected from phenyl and a 5- or 6-membered heterocyle, wherein phenyl and heterocycle are substituted with 0-5 R^{Ja}.

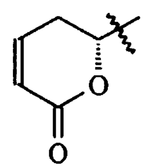
In certain preferred embodiments, B is selected from phenyl, a 6-membered lactone ring, and a heterocycle selected from 2-pyrrolidonyl, 2H-pyrrolyl, 4-piperidonyl, 6H-1,2,5-thiadiazinyl, *2H,6H*-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, morpholinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, tetrahydrofuranyl, *6H*-1,2,5-

thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazole, wherein the phenyl, lactone ring, and heterocycle are substituted with 0-5 $R^{J'}$.

In certain preferred embodiments, B is selected from phenyl, pyridinyl, and a 6-membered lactone ring selected from the formulas:



and



wherein the phenyl, pyridinyl, and lactone ring is substituted with 0-3 R^{Ja}.

In certain preferred embodiments, A is CH_2CH_2 substituted with 0-1 OH and R^{Ja} is selected from OH and methyl. In certain preferred embodiments, R_{40b} is hydrogen. In certain preferred embodiments, R_{25b} and R_{25c} are hydrogen.

In certain preferred embodiments, R_{25b} and R_{25c} are independently selected from hydrogen, $S(O)_2R^b$, C_{1-6} alkyl, fluorenyl, and $(CH_2)_r$phenyl, wherein the alkyl and phenyl are substituted with 0-2 R_{25d};

R^b is selected from C_{1-6} alkyl, phenyl, benzyl, and phenethyl wherein R^b is substituted with 0-3 R^e;

R_{25d}, at each occurrence, is selected from hydrogen, F, Cl, Br, I, OH, OC_{1-6} alkyl, NO_2, CN, CF_3, CH_3, CO_2H, CO_2C_{1-6} alkyl, $OC(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $OC(=O)NH_2$, NH_2, NHC_{1-6} alkyl, $N(C_{1-6}$ alkyl$)_2$ phenyl, phenoxy, benzoyl, and pyridinyl wherein phenyl, phenoxy, benzoyl, and pyridinyl are substituted with 0-3 R^e; and

R^e is selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, and NH_2.

In certain preferred embodiments, R_{25b} is hydrogen and R_{25c} is selected from $S(O)_2C_{1-6}$ alkyl, C_{1-6} alkyl, fluorenyl, $S(O)_2$phenyl substituted with 0-3 R_{25d} selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, and NH_2; and phenyl substituted with 0-3 R_{25d} selected from phenyl, phenoxy, and benzoyl, wherein phenyl, phenoxy, and benzoyl are substituted with 0-3 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, and NH_2.

In certain preferred embodiments, R_{40b} is selected from hydrogen, C_{1-6} alkyl, $(CH_2)_rOC(=O)$phenyl, and $(CH_2)_r$phenyl, wherein the alkyl, $(CH_2)_rOC(=O)$phenyl, and phenyl are substituted with 0-3 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, phenyl, phenoxy, and benzoyl; and r is selected from 1 and 2.

In certain preferred embodiments, R_{40b} is selected from hydrogen, CH_2, CH_2CH_2, $CH_2CH_2CH_2$, and $(CH_2)_r$phenyl, wherein the CH_2, CH_2CH_2, $CH_2CH_2CH_2$, and phenyl are substituted with 0-1 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, phenyl, phenoxy, and benzoyl.

In certain preferred embodiments, R_{40b} is selected from hydrogen, C_{1-6} alkyl, $(CH_2)_rOC(=O)$phenyl, and $(CH_2)_r$phenyl, wherein the alkyl, $(CH_2)_rOC(=O)$phenyl, and phenyl are substituted with 0-3 R^e;

R_{25b} and R_{25c} are independently selected from hydrogen, $S(O)_2R^b$, C_{1-6} alkyl, fluorenyl, and $(CH_2)_r$phenyl, wherein the alkyl and phenyl are substituted with 0-2 R_{25d};

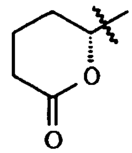
R^b is selected from C_{1-6} alkyl, phenyl, benzyl, and phenethyl wherein R^b is substituted with 0-3 R^e;

R_{25d}, at each occurrence, is selected from hydrogen, F, Cl, Br, I, OH, OC_{1-6} alkyl, NO_2, CN, CF_3, CH_3, CO_2H, CO_2C_{1-6} alkyl, $OC(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $OC(=O)NH_2$, NH_2, NHC_{1-6} alkyl, $N(C_{1-6}$ alkyl$)_2$ phenyl, phenoxy, benzoyl, and pyridinyl wherein phenyl, phenoxy, benzoyl, and pyridinyl are substituted with 0-3 R^e; and

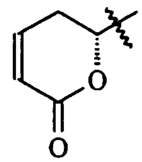
R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, phenyl, phenoxy, and benzoyl;

A is CH_2CH_2 substituted with 0-1 OH;

B is selected from phenyl, pyridinyl, and a 6-membered lactone ring selected from the formulas:



and



wherein the phenyl, pyridinyl, and lactone ring is substituted with 0-3 R^{Ja} selected from OH and methyl; and r is selected from 1 and 2.

In other embodiments, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt thereof.

In other embodiments, the present invention provides methods for stabilizing microtubules, the method comprising administering to a patient, preferably in need thereof, a therapeutically effective amount of a compound described herein.

DEFINITIONS

As used herein, the following terms and expressions have the indicated meanings. It will be appreciated that the compounds of the present invention may contain asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry

or isomer form is specifically indicated.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Stable compounds are preferred in accordance with the present invention.

The compounds disclosed herein may be substituted or unsubstituted. "Substituted" is intended to indicate that one or more hydrogens of the identified moiety is replaced with a selection from the indicated group(s), provided that the normal valency in the identified moiety is not exceeded, and that the substitution results in a stable compound. When a substituent is =O (a keto group), then two hydrogens on the implicated carbon atom are replaced. By way of illustration, when a carbon ring containing one oxygen is substituted on the carbon adjacent to the oxygen =O, a lactone is formed.

Alkyl, alkenyl, and alkynyl groups include both straight and branched carbon chains. Thus, as used herein, the term "C_{1-6} alkyl", for example, is meant to encompass both straight and branched alkyl chains containing a total of 6 carbon atoms. Alkenyl groups according to the invention are straight chain or branched chain hydrocarbons that include one or more carbon-carbon double bonds. Preferred alkenyl groups are those having 2 to about 10 carbon atoms. Alkynyl groups according to the invention are straight or branched chain hydrocarbons that include one or more carbon-carbon triple bonds. Thus, alkyl, alkenyl, and alkynyl groups according to the invention include, but are not limited to, hydrocarbons such as methyl, ethyl, ethene, ethyne, propyl, propene, propyne, butyl, pentyl, isopropyl, 2-butyl, isobutyl, 2-methylbutyl, and isopentyl moieties having 1 to about 10 carbon atoms, preferably 1 to about 6 carbon atoms.

Cycloalkyl groups are cyclic hydrocarbons having 3 to about 10 carbon atoms such as cyclopentyl and cyclohexyl

groups. Examples include, but are not limited to cyclopropyl, cyclobutyl, or cyclopentyl.

Aryl groups according to the invention are aromatic and heteroaromatic groups having 6 to about 14 carbon atoms, preferably from 6 to about 10 carbon atoms, including, for example, naphthyl, phenyl, indolyl, and xylyl groups and substituted derivatives thereof, particularly those substituted with amino, nitro, hydroxy, methyl, methoxy, thiomethyl, trifluoromethyl, mercaptyl, and carboxy groups. Alkaryl groups are groups that contain alkyl and aryl portions and are covalently bound to other groups through the alkyl portion, as in a benzyl group. Alkheteroaryl groups are groups that contain alkyl and heteroaryl portions and are covalently bound to other groups through the alkyl portion.

As used herein, "carbocycle" is intended to mean any stable monocyclic ring, which may be saturated or partially unsaturated. Preferably, carbocycles are 3- to 12-membered, more preferably, 3- to 6- membered. Thus, the term carbocycle includes cycloalkyl groups and single, fused or bi- or tri-cyclic groups wherein the ring(s) is entirely of carbon atoms. Examples of such carbocyles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl (tetralin).

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl groups.

"Heterocycle", "heterocyclic ring", or "heterocycloalkyl" as those terms are used herein, are intended to mean a stable ring, which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 3 heteroatoms independently selected from the group consisting of N, O and S. Thus, the

term heterocycle includes aromatic and non-aromatic groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. Heterocycle includes aromatic heterocyclic systems which consists of carbon atoms and from 1 to 3 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Preferably, the heterocycles of the present invention are stable 5- to 6- membered monocyclic heterocyclic rings, which may be aromatic or non-aromatic.

Examples of heterocycles include, but are not limited to, 2-pyrrolidonyl, 2H-pyrrolyl, 4-piperidonyl, 6H-1,2,5-thiadiazinyl, 2*H*,6*H*-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, morpholinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, tetrahydrofuranyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl. Preferred heterocycles include, but are not limited to, pyridinyl,

furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, and oxazolidinyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The present invention contemplates the compounds disclosed herein to be used as prodrugs. The term "prodrug" is intended to include any molecule that is transformed into a compound according to formula (I) or any other compound of the present invention *in vivo* following administration to a mammal. A prodrug form of a compound of the present invention can be prepared, for example, by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein the hydroxy or amino group is bonded to any group that, when the prodrug is administered to a mammal subject, cleaves to form a free hydroxyl or free amino, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention, and the like.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective produce the desired effect. Such effects include, for example, the stablization of microtubules.

The compounds of the present invention may be used as drugs in connection with pharmaceutically acceptable carriers. The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

The target compounds and intermediates of the present invention may contain protecting groups. Protecting groups are known *per se* as chemical functional groups that can be selectively appended to and removed from functionality, such as hydroxyl and amine groups, present in a chemical compound to render such functionality inert to certain chemical reaction conditions to which the compound is exposed. *See, e.g.*, Greene and Wuts, Protective Groups in Organic Synthesis, 2d edition, John Wiley & Sons, New York, 1991. Numerous hydroxyl protecting groups are known in the art, including the acid-labile t-butyldimethylsilyl, diethylisopropylsilyl, and triethylsilyl groups and the acid-stable aralkyl (*e.g.*, benzyl), triisopropylsilyl, and *t*-butyldiphenylsilyl groups. Useful amine protecting groups include the allyloxycarbonyl (Alloc), benzyloxycarbonyl (CBz), chlorobenzyloxycarbonyl, t-butyloxycarbonyl (Boc), fluorenylmethoxycarbonyl (Fmoc), isonicotinyloxycarbonyl (I-Noc) groups.

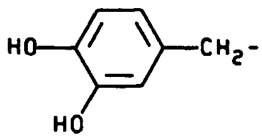
As used herein, the term "oxidatively labile group" is intended to include all groups known to be removed by an oxidizing agent. An example of an oxidizing agent includes, but is not limited to, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

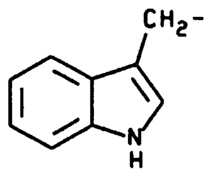
The term amino acid as used herein is intended to include all naturally-occurring and synthetic amino acids known in the art. In general, amino acids have structure $H_2N\text{-}CH(R_C)\text{-}C(O)OH$ where R_C is the amino acid side chain. Representative, naturally-occurring side chains are shown in Table 1.

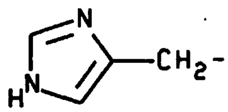
TABLE 1

CH_3-	CH_3-CH_2-S-CH_2-CH_2-
HO-CH_2-	HO-CH_2-CH_2-
C_6H_5-CH_2-	CH_3-CH_2(OH)-

$HO-C_6H_5-CH_2-$







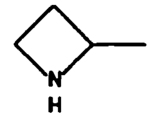
$HS-CH_2-$

$HO_2C-CH(NH_2)-CH_2-S-S-CH_2-$

CH_3-CH_2-

$CH_3-S-CH_2-CH_2-$

$HO_2C-CH_2-NH_2C(O)-CH_2-$



$HCO_2-CH_2-CH_2-$

$NH_2C(O)-CH_2-CH_2-$

$(CH_3)_2-CH-$

$(CH_3)_2-CH-CH_2-$

$CH_3-CH_2-CH_2-$

$H_2N-CH_2-CH_2-CH_2-$

$H_2N-C(NH)-NH-CH_2-CH_2-CH_2-$

$H_2N-C(O)-NH-CH_2-CH_2-CH_2-$

$CH_3-CH_2-CH(CH_3)-$

$CH_3-CH_2-CH_2-CH_2-$

$H_2N-CH_2-CH_2-CH_2-CH_2-$

Hydrophobic amino acid side chains are preferred, including the CH_3-, $C_6H_5-CH_2-$, CH_3-CH_2-, $CH_3-S-CH_2-CH_2-$, $(CH_3)_2-CH-$, $(CH_3)_2-CH-CH_2-$, $CH_3-CH_2-CH(CH_3)-$, and $CH_3-CH_2-CH_2-CH_2-$ side chains. Peptides according to the invention are linear, branched, or cyclic chemical structures containing at least 2 covalently bound amino acids.

It will be appreciated that groups according to the invention can be unsubstituted or can bear one or more substituents.

Certain compounds of the invention contain amino groups and, therefore, are capable of forming salts with various inorganic and organic acids. Such salts are also within the scope of this invention. Representative salts include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, heptanoate,

hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, succinate, sulfate, tartrate, tosylate, and undecanoate. The salts can be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is later removed *in vacuo* or by freeze drying. The salts also can be formed by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The compounds of the present invention can be admixed with carriers, excipients, and/or diluents to form novel compositions. Such compositions can be used in prophylactic, diagnostic, and/or therapeutic techniques. By administering an effective amount of such a composition, prophylactic or therapeutic responses can be produced in a human or some other type mammal. It will be appreciated that the production of prophylactic or therapeutic responses includes the initiation or enhancement of desirable responses, as well as the mitigation, cessation, or suppression of undesirable responses. The compositions of the invention are expected to find use, for example, in the inhibition of undesired cell proliferation (*e.g.*, cancer) and in the inhibition of rejection in organ transplantation procedures. (*See, e.g.*, Longley, *et al.*, *Transplantation* **1991**, *52*, 650 and 656).

Compositions of the invention can be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980). The compositions can include a compound of the invention as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable, for example, for oral administration. Other suitable modes of administration will be apparent to

those skilled in the art. The compound of the invention can be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, solutions, suppositories, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The compound of the invention is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in appropriately soluble (*e.g.*, gelatin) capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols.

When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, glycerin and various like combinations thereof.

For parenteral administration, suspensions containing a compound of the invention in, for example, aqueous propylene glycol can be employed. The suspensions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. The aqueous suspensions are suitable for intravenous injection purposes. The preparation of such suspensions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Additionally, it is possible to administer the compounds of the invention topically and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The compounds of the invention can be employed as the sole active agent in a pharmaceutical composition or can be used in combination with other active ingredients, *e.g.*, other agents useful in diseases or disorders.

The amount of active ingredient that is to be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. The specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects provided that such higher dose levels are first divided into several small doses for administration throughout the day.

The concentrations of the active ingredient in therapeutic compositions will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (*e.g.*, hydrophobicity) of the active ingredient, and the route of

administration. Typical dose ranges are from about 285 μg/kg of body weight per day in three divided doses; a preferred dose range is from about 42 μg/kg to about 171 μg/kg of body weight per day. The preferred dosage to be administered is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration, as well as other factors, including bioavailability, which is in turn influenced by several factors well known to those skilled in the art.

The present invention includes the use of a discodermolide or a mimic thereof, such as Formula I-a, in combination therapy with another agent, including, but not limited to, Taxol®. Thus, component (a) discodermolide or a mimic thereof and component (b) Taxol may be formulated together, in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.) as a combination product. When component (a) and (b) are not formulated together in a single dosage unit, the component (a) may be administered at the same time as component (b) or in any order; for example component (a) of this invention may be administered first, followed by administration of component (b), or they may be administered in the revserse order. If component (b) contains more than one agent, these agents may be administered together or in any order. When not administered at the same time, preferably the administration of component (a) and (b) occurs less than about one hour apart. Preferably, the route of administration of component (a) and (b) is oral. The terms oral agent, oral inhibitor, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that component (a) and component (b) both be administered by the same route (that is, for example, both orally) or dosage form, if desired, they may each be administered by different routes

(that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously) or dosage forms.

As is appreciated by a medical practitioner skilled in the art, the dosage of the combination therapy of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

The proper dosage of components (a) and (b) of the present invention will be readily ascertainable by a medical practitioner skilled in the art, based upon the present disclosure. By way of general guidance, typically a daily dosage may be about 100 milligrams to about 1.5 grams of each component. If component (b) represents more than one compound, then typically a daily dosage may be about 100 milligrams to about 1.5 grams of each agent of component (b). By way of general guidance, when the compounds of component (a) and component (b) are administered in combination, the dosage amount of each component may be reduced by about 70-80% relative to the usual dosage of the component when it is administered alone as a single agent for the treatment of HIV infection, in view of the synergistic effect of the combination.

The combination products of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized. In order to minimize contact, for example, where the product is orally administered, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is

not released in the stomach but rather is released in the intestines. Another embodiment of this invention where oral administration is desired provides for a combination product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component. In each formulation wherein contact is prevented between components (a) and (b) via a coating or some other material, contact may also be prevented between the individual agents of component (b).

All reactions were carried out in oven-dried or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon before use. Dichloromethane, benzene and diisopropyl amine were freshly distilled from calcium hydride before use. Triethylamine and diisopropylethylamine were distilled from calcium hydride and stored over potassium hydroxide. Hexamethylphosphoramide was freshly distilled from calcium hydride. Anhydrous pyridine, dimethylformamide and dimethyl sulfoxide were purchased from Aldrich and used without purification. *n*-Butyllithium and *t*-butyllithium were purchased from Aldrich and standardized by titration with diphenylacetic acid.

Unless stated otherwise all reactions were magnetically stirred and monitored by thin layer chromatography using 0.25 mm E. Merck pre-coated silica gel plates. Flash column chromatography was performed with the indicated solvents using silica gel-60 (particle size 0.040-0.062 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

All melting points were determined on a Bristoline heated-stage microscope or a Thomas-Hoover apparatus and are corrected. The IR and NMR were obtained for $CHCl_3$ and $CDCl_3$ solutions respectively unless otherwise noted. Infrared spectra were recorded with a Perkin-Elmer Model 283B spectrometer using polystyrene as an external standard. Proton NMR spectra were recorded on a Bruker AM-500 spectrometer. Carbon-13 NMR spectra were recorded on a Bruker AM-500 or AM-250 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (d 0.00) for proton and chloroform δ 77.0) or benzene (δ 128.0) for carbon-13.

Optical rotations were obtained with a Perkin-Elmer model 241 polarimeter in the solvent indicated. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on either a VG micromass 70/70H high resolution double-focusing electron impact/chemical ionization spectrometer or a VG ZAB-E spectrometer. Microanalyses were performed by Robertson Laboratories, Madison, New Jersey. Single-crystal X-ray diffraction structure determination were performed at the University of Pennsylvania using an Enraf Nonius CAD-4 automated diffractometer. High performance liquid chromatography (HPLC) was performed using a Ranin component analytical/semi-prep system.

All drugs were dissolved in sterile DMSO and stored at $^-20°C$. Microtubule protein (MTP) was purified by 2 cycles of temperature-dependent assembly-disassembly from calf brain and stored in liquid nitrogen. *See*, for example, Welsenberg, R.C., "Microtubule formation in vitro in

solutions containing low calcium concentrations", *Science*, **1972**, 177, 1104-1105. The concentration of tubulin in the microtubule protein preparation was approximately 85%.

SYNTHESIS

All processes described herein are contemplated to be run on any scale, including milligram, gram, kilogram, and commercial scale.

It has been found in accordance with the present invention that the synthesis of polyhydroxy, dienyl lactones such as the discodermolides can be achieved by highly convergent and stereocontrolled synthetic procedures.

As shown in Figure 1 for the (-)-discodermolide antipode, our analysis revealed a repeating triad of contiguous stereocenters, separated by Z-olefinic linkages at C(8,9) and C(13,14). Disconnections at C(8,9), C(14,15) and C(21,22) generated fragments **A**, **B** and **C**, each deriving in turn from a common precursor (**5**) containing the recurring stereochemical triad.

As shown in Figure 2, precursor **5** was prepared by a synthetic procedure whereby hydroxy ester (-)-**6** was protected as the *p*-methoxybenzyl (PMB) ether by treatment with the Bundle trichloroimidate reagent **7** under acidic conditions. Reduction with $LiAlH_4$ provided the alcohol (-)-**8** after distillation. Swern oxidation, Evans aldol condensation, and Weinreb amide formation completed the construction of common precursor (+)-**5**. This concise five-step synthesis could be routinely carried out on a 50-g scale in 59% overall yield.

Alternatively, as shown in Figure 37, Swern oxidation of **(+)-8** followed by the addition norephedrine derived oxazolidinone 61 results in a crystalline product **62** which, in turn, can be converted to common precursor (-)-**5**.

In view of the polypropionate structure of the **A** fragment, we performed a second asymmetric aldol reaction, as shown in Figure 3. Initial formation of the *p*-methoxybenzylidene acetal (-)-**11** from common precursor (-)-**5** (78% yield) was designed to allow selective deprotection of C(21) and C(19) hydroxyls for introduction of the terminal diene and carbamate moieties. Following reduction of amide (-)-**11** to the aldehyde (80% yield), (aldol reaction with oxazolidinone (+)-**9** (80% yield) provided alcohol (+)-**13** which incorporated the five stereocenters of subunit **A**. The structure of (+)-**13** was confirmed by single-crystal X-ray analysis. Protection of the secondary alcohol as the TBS ether and removal of the chiral auxiliary ($LiBH_4$,EtOH,THF) afforded primary alcohol (-)-**15** (81% yield, two steps), which could be efficiently converted either to tosylate (-)-**16** or iodide (-)-**A**.

As outlined in Figure 1, our strategy required a Z vinylic halide **B** for coupling with fragment **A**. Beginning again with the common precursor (+)-**5**, TBS protection (Figure 4) followed by reduction of the Weinreb amide [DIBAL (2 equiv), THF, -78 °C](Kim, *et al., Tetrahedron Lett.* **1989**, *30*, 6697) afforded aldehyde (+)-**18** in 88% yield for the two steps. We adopted a stepwise approach to introduction of the vinyl halide, whereby (+)-**18** was converted to the Z α-bromo unsaturated ester (-)-**19** ($Ph_3PCBrCO_2Et$, PhH, reflux; 75% yield after chromatography). Reduction to allylic alcohol (-)-**20** followed by mesylation and displacement with $LiBHEt_3$ then furnished Z vinyl bromide (-)-**22** in 77% overall yield from **19**.

One preferred synthetic strategy utilized a vinyl iodide as the desired **B** segment. Synthesis of (-)-**B** was achieved by direct olefination of aldehyde (+)-**18** (41%, 6:1 Z/E) (Figure 9), followed by chromatographic removal of the

undesired E product. Alternatively, the B segment can be prepared by the two routes shown in Figure 39. The first involves an α-iodo sulfone **69** to effect a one-step installation of the vinyl iodide. The second exploits the enhanced reactivity of the trans iodide of diiodide **70**.

Our preferred synthetic strategy involves selective removal of a primary PMB ether in the presence of a PMP acetal in the **AB** coupling product ((-)-**39**, Figure 5). A 1:1 mixture of PMB ether (-)-**22** and PMP acetal (-)-**15** was exposed to DDQ (1.1 equiv) in CH_2Cl_2/H_2O (Figure 6). The acetal (-)-**15** largely remained intact while the debenzylated alcohol (-)-**25** was formed in 83% yield.

As shown in Figure 7, we again utilized the TBS ether (+)-**17** for the preparation of **C** from common precursor (+)-**5**. Oxidative cleavage of the PMB group (DDQ, CH_2Cl_2, H_2O) provided alcohol **26** in variable (60-86%) yields, accompanied by the corresponding lactone. Hydrogenolysis with Pearlman's catalyst afforded (+)-**26** in 92% yield. Exposure of the alcohol to SO_3.pyr furnished aldehyde (+)-**27** (98% yield), which in turn was converted to dithiane (+)-**28** (79%). In the latter step, our modification of the Evans protocol for dithiane generation [$(TMSSCH_2)_2CH_2$, $ZnCl_2$, Et_2O] minimized elimination of the TBS ether to form the α,β-unsaturated amide. Following reduction to aldehyde (+)-**29** with DIBAL (91% yield), dimethyl acetal formation gave (+)-**30** (99%). The coupling of dithiane **30** with *R*-(-)-glycidyl benzyl ether [(-)-**31**] then afforded alcohol (-)-**32** in 79% yield. Unmasking of the ketone moiety [$(CF_3CO_2)_2IPh$, 80%] and Evans stereocontrolled reduction (97%) provided the anti diol (-)-**34**, which embodied all of the stereocenters in fragment **C**.

Acid-catalyzed cyclization of (-)-**34** (TsOH, room temperature) provided methoxy pyran **35** in 87% yield as a 1:2

mixture of α and β anomers (Figure 8). Debenzylation (H_2, Pd/C) of **36** afforded alcohol **37** quantitatively. Exposure to EtSH and $MgBr_2$ in Et_2O then gave a separable 6:1 mixture of β ethyl hemithioacetal (+)-**38** and its α anomer in 83% yield. Swern oxidation of (+)-**38** furnished the final fragment (+)-**C** in 86% yield.

Reaction of (-)-**B** with the organozinc derivative of (-)-**A** (Figure 10) was achieved by premixing iodide **A** with dried solid $ZnCl_2$ (ether, -78 °C) before addition of *t*-BuLi. It is believed that three equivalents of *t*-BuLi are required for complete consumption of (-)-**A**, probably because the first equivalent reacts with $ZnCl_2$. This modification increased the yield to 66% after flash chromatography.

Conversion of the Z trisubstituted olefin (-)-**39** to the phosphonium iodide (-)-**49** began with selective removal of the PMB group, as in our model study (DDQ, CH_2Cl_2, H_2O), furnishing (-)-**40** in 87% yield (Figure 11). As shown in Figure 12, alcohol (-)-**40** furnished the requisite iodide **42** almost exclusively, as indicated by NMR examination of the crude material. The very sensitive iodide was used without purification. Thorough mixing of iodide **42** with *I*-Pr_2NEt (3 equiv) followed by exposure to excess PPh_3 (15 equiv) without solvent at 80 °C generated (-)-**49** in 37% yield for the two steps. The major by-product was characterized as (-)-**50** (35% yield). The unsaturated model alcohol (+)-**44** similarly afforded the Wittig salt (+)-**46** in low yield (Figure 13), whereas the saturated derivative (+)-**51** gave phosphonium iodide (+)-**53** almost quantitatively.

Our preferred method to prepare compound **49** entails the mixing of iodide **42** with *I*-Pr_2NEt (0.5 equiv.) and PPh_3 (4 equiv.) in benzene/toluene (7:3) and subjecting this mixture to an applied pressure of 10-15 Kbar.

As shown in Figure 14, assembly of the discodermolide backbone entailed Wittig coupling of aldehyde **C** with the ylide derived from **AB** phosphonium salt (-)-**49** to install the C(8,9) Z alkene in (-)-**54** (>49:1 Z/E, 76% yield). DIBAL reduction (88% yield) followed by oxidation of the resultant primary alcohol (-)-**55** then produced aldehyde (-)-**56** (96%). The terminal Z diene (-)-**57** was elaborated via the Yamamoto protocol in 70% yield with excellent selectivity (16:1 Z/E). After flash chromatography, hydrolysis of the hemithio acetal and mild DMSO/Ac_2O oxidation provided lactone (-)-**58** in 82% yield for the two steps. Removal of the PMB group (DDQ, CH_2Cl_2, H_2O, 95% yield) and carbamate formation (Cl_3CONCO, CH_2Cl_2, neutral Al_2O_3, 83%) afforded tris(TBS ether) (-)-**60**. Final deprotection with 48% HF/CH_3CN (1:9) furnished (-)-discodermolide, identical with an authentic sample (Figure 15).

Alternatively, lactone **58** can be prepared by the Wittig coupling of aldehyde **67** with the ylide derived from **49**, as shown in Figure 42. Regioselective ring opening of benzylidene acetal **76** with DIBAL followed by oxidation with pyridinium dichromate affords aldehyde **77**. Application of the Yamamoto olefination protocol affords compound **58**. Alternatively, the diene installation can be effected using an alkyl chromium reagent generated by the procedure of Hodgson, *et al.*, *Tetrahedron Letters* **1992**, *33*, 4761. The aldehyde **67** can be prepared by from compound (-)-**27** (prepared generally according to the procedure of Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) by effecting a Mukaiyama aldol reaction between aldehyde **27** and enol ether **63** to form enone **64**. Reduction of enone **64** furnished a 9:1 mixture of carbinols, favoring the desired isomer. Protection of the newly formed carbinol with TBSCl and subsequent ozonolysis of the trisubstituted olefin provides

67 in approximately 80% overall yield, as shown in figure 38..

Alternatively, the discodermolide backbone can be synthesized by installing the terminal diene before Wittig coupling with Fragment **C**. As shown in Figure 40, regioselective ring opening of benzylidine acetal **39** with DIBAL-H followed by oxidation and application of the Yamamoto olefination protocol provides diene **73**. Selective removal of the less hindered PMB using DDQ/H_2O is followed by conversion to the primary iodide and phosphonium salt **75**. Alternatively, the primary PMB can be enhanced for either a dimethoxy benzyl ether or silyl protecting group earlier in the sequence. Application of Dauben's high pressure conditions results in approximately 75% yield of the desired phosphonium salt.

Further assembly of the discodermolide backbone entails Wittig coupling of aldehyde **67** with the ylide derived from phosphonium salt **75** to afford **58**. Further manipulation as indicated above (Figure 15) provides **(+)**-discodermolide.

Another preferred route to phosphonium salt **75** is depicted in Figures 43 and 44. Starting from alcohol **40**, trityl ether **87** may be prepared by contacting with trityl chloride and N,N-dimethyl-pyridine (DMAP) in hot pyridine (Figure 43). Reductive opening of the anisylidine acetal functionality of **87** with DIBALH provides the primary alcohol **88**. Oxidation of **88** with Dess-Martin Periodane (DMP) followed by Yamamoto olefination provides diene **90** with approximately a 8-11:1 diastereoselectivity.

The trityl protecting group of **90** is preferably removed utilizing a modified Boeckman protocol, as described, for example, in Boeckman, R. K., Jr.; Potenza, J. C. *Tetrahedron Lett.* 1985, 26, 1411, the disclosure of which is hereby incorporated by reference in its entirety, to provide alcohol **74**. (Figure 44). Wittig salt **75** may be prepared

via conversion of alcohol **74** to the corresponding iodide employing a modified Corey protocol (PPh_3, I2, PhH/Et2O) and subjection of the unstable iodide to excess PPh_3 at high pressure (12.8 Kbar) in a buffered, non-polar medium (Hunig's base,toluene/benzene).

Treatment of tetraene **58** (a mixture of diene isomers; *ca* 8-12:1) with DDQ results in oxidative removal of the PMB ether and, selective destruction of the trans-diene impurity preferably yields diastereomerically pure alcohol **59** after flash chromatography (Figure 45).

Alcohol **59** may be subjected to the Kocovsky protocol to yield the carbamate **60** (Scheme 46). Carbamate **60** is preferably taken onto the natural product (+)-discodermolide by slow addition of acid, for example, 3N HCl to a methanol solution of **60** over a suitable time period such as 12 hours. Discodermolide may be purified by flash chromatography followed by crystallization from, for example, neat acetonitrle.

An Aldol reaction between aldehyde **92** and the corresponding enolate of amide **93** yields the common precursor 5 in three steps (Figure 47). Amide **93** can be easily prepared from the commercially available acid chloride **94** (Figure 48).

Alternative synthetic routes to tetraene **58** are depicted in Figures 49 and 50. A palladium catalyzed coupling between vinyl iodide **96** and organozinc **97** yields **58** (Figure 49). The organozinc **97** may be prepared, for example, from common iodide intermediate **97a** (Figures 63 and 64). As will be appreciated by the accompanying figures, iodide **97a** may be obtained via a protected (i.e., trityl-protected) alcohol (Figure 63) using chemistry similar to that provided in Figure 43. Alternatively, iodide **97a** may be obtained through chemistry wherein the intermediates in route to **97a** bear a chiral auxiliary (Figure 64, **97a**).

Alternate synthetic routes to mimics of discodermolide, such as compounds of formula I-a, include triply convergent approaches (Figure 64). In this regard, it will be appreciated that the overall polyproprionate structure of (+)-discodermolide typically contains Z-olefinic linkages at C8-C9, C13-C14, and C21-C22, in addition to the carbamate and/or lactone moieties (Figure 56).

Preferred modifications of the discodermolide structure include deletion of the C14 methyl group, generating a Z-disubstituted olefin instead of the Z-trisubstituted olefin at C13-C14. Modification of the C1-C14 region of discodermolide results in compounds referred to herein as "C14 normethyl" analogs. Such compounds may be synthesized, for example, by the methods taught in Smith, A.B., III, et al., "Gram-scale synthesis of (+)-discodermolide", *Org. Lett.*, **1999**, 1, 1823-1826 and Smith, A.B., III, et al., "Evolution of a gram-scale (+)-discodermolide", *J. Am. Chem. Soc.*, **2000**, 122 8654-8664. In addition, a late stage Wittig olefination installs a variety of C1-C8 structure motifs which permit further synthetic transformation in this region.

The construction of other potentially important C1-C14 analogs may be accomplished through several advanced intermediates. For example, following late stage Wittig olefination leading to discodermolide or an analog thereof (Figure 54), there is high selectivity *(Z/E* 24/1) favoring the Z-olefin **58** (69% yield). Intermediate **58** may subsequently be carried on to a (+)-discodermolide derivative in, for example, 86% yield for 3 steps. The olefin geometry at C8-C9 may be manipulated by employing the minor *E*-olefinic isomer using essentially the same strategy. Oxidative removal of the paramethoxbenzyl group with DDQ affords the corresponding alcohol in, for example, 52% yield, which may then be subjected to the Kocovsky protocol to install the carbamate. *See*, for example, procedures described in Kocovsky, P., "Carbamates: a method of

synthesis and some synthetic applications", *Tetrahedron Lett.*, **1986**, 27, 5521-5524. Global desilylation furnishes the C(8,9) *E* analog (-)-**I-iv**, in, for example, yields of approximately 95% for 2 steps.

Another minor byproduct may result during the final global deprotection of **58** to (+)-discodermolide or a derivative thereof. Although the acidic conditions (3N HCl, MeOH) may lead to the desired product reliably and in good yield (93%), the minor byproduct available due to the large scale synthesis may be the α,β-unsaturated lactone, which can be obtained after purification by HPLC and recrystallization (CH_3CN). The structure may be secured by single crystal X-ray analysis if desired.

Analogs along the C1-C8 backbone also include, for example, compounds referred to herein as "deletion analogs." In this regard, a reliable route to terminal olefin (+)-**67a** (Figure 55) is straightforward in view of the optimization of (-)-**67** described in Smith, A.B., III, et al., *J. Am. Chem. Soc.*, **2000**, 122 8654-8664. As such, a general synthesis of analogs deoxygenated at C7 is available. By way of illustration, hydroboration of the terminal olefin using the Evans protocol described in *J. Am. Chem. Soc.*, **1992**, 114, 667 1 6679, provides (-)-**67b** (70%). Parikh-Doering oxidation as described in *J Am. Chem. Soc.*, **1967**, 89, 5505-5507, furnishes aldehyde (-)-**67c** (80%). Although Wittig olefination (Figure 54) typically results in a modest yield (8%) of the **Z**-olefin **58a**, the synthesis of the C7 deoxygenated analogs may be completed by these procedures. For example, removal of the PMB group (DDQ, H_20, 99%), followed by installation of the carbamate via the Kocovsky protocol, furnishes the carbamate of discodermolide or its analogs.

The C14-normethyl analog of discodermolide (i.e., (+)-**I-ii**, Figure 57), possessing a C8-C9 *Z*-olefin, may also be prepared as described herein. During the Wittig reaction to

introduce the *Z*-olefin linkage, however, the vigorous conditions required to generate the phosphonium salt **75** (Figure 54) may result in an intramolecular cyclization involving the C13-C14 trisubstituted olefin. Smith, A.B., III, et al., "Total synthesis of discodermolide", *J Am. Chem. Soc.*, **1995**, 117, 12011-12012 and Harried, S.S., et al., "Total synthesis of discodermolide: an application of a chelation-controlled alkylation reaction", *J Org. Chem.*, **1997**, 62, 6098-6099. Generation of the Wittig salt at high pressure may circumvent this problem. *See*, for example, Smith, A.B., III, et al., "Evolution of a gram-scale (+)-discodermolide", *J. Am. Chem. Soc.*, **2000**, 122 8654-8664. For certain compounds wherein the trisubstituted olefin is replaced with a cis-disubstituted olefin such as **75a** (Figure 54), the need for high pressure may be negated and thereby significantly simplify the overall synthetic strategy.

Preparation of the C14-normethyl analogs may be accomplished via a Stork-Zhao olefination as described in Stork, G., et al., "A stereoselective synthesis of (Z)-1-iodo-1-alkenes", *Tetrahedron Lett.*, **1989**, 30, 2173-2174 of aldehyde (-)-**18** (Figure 58), prepared by methods described in *J. Am. Chem. Soc.*, **2000**, 122 8654-8664, furnishes vinyl iodide (+)-**B(3)a** (13:1 *Z/E*; 73%). Negishi cross-coupling by procedures described in *J Am. Chem. Soc.*, **1980**, 102, 3298-3299, with iodide (+)-**A2**, prepared by methods described in *J. Am. Chem. Soc.*, **2000**, 122 8654-8664, furnishing, for example, olefin (+)-**39a**. To facilitate the required discrimination of the C19-hydroxyl, a protecting group interchange may be used. For example, the PMB group in (+)-**39a** may be removed chemoselectively (DDQ, H_2O, 80%) and replaced with a trityl moiety (tritylchloride, DMAP, pyr. 81%) to provide (+)-**87a**.

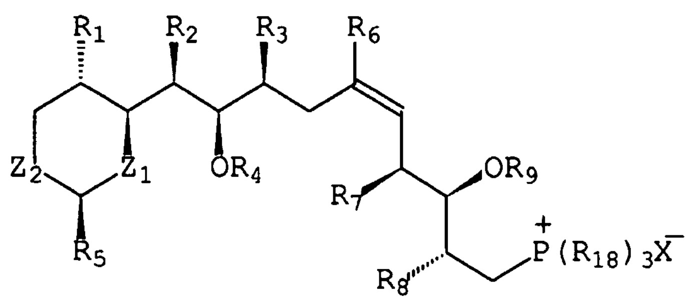
Installation of the C21-C24 terminal *Z*-diene (Figure 58) typically begins with reductive opening of acetal (+)-**87a** with DIBAL as described in Takano, S., et al., "A facile cleavage of benzylidene acetals with diisobutylaluminum hydride", *Chem. Lett.*, **1983**, *10*, 1593-1596, followed by Dess-Martin oxidation as described in Dess, D.B. et al., "A useful 12-1-5 triacetoxyperiodinane (the Dess Martin periodinane) for the selective oxidation of primary or secondary alcohols and a variety of related 12-1-5 species", *J Am. Chem. Soc.*, **1991**, 113, 7277-7287. The resulting aldehyde may then be subjected to Yamamoto diene synthesis as described in Ikeda, Y., et al., "Stereoselective synthesis of (Z)-and (E)-1, 3-alkadienes from aldehydes using organotitanium and lithium reagents", *Tetrahedron*, **1987**, 43, 723-730 to furnish **90a** (10:1 *Z/E*) in approximately 63% yield for 2 steps. Removal of the minor *E*-diene isomer may be accomplished at a later stage of the synthesis as described in *J. Am. Chem. Soc.*, **2000**, 122 8654-8664. The trityl group may be removed, for example, by procedures described in Boeckman, R.K., Jr., et al., "Catecholboron halides: mild and selective reagents for cleavage of common protecting groups", *Tetraahedron Lett.*, **1985**, 26, 1411-1414 (i.e., with chlorocatecholborane, 80%), preferably followed by conversion of the resulting alcohol to the iodide with Ph_3P, I_2, PhH/Et_2O as described in Corey, E.J., et al., "Total synthesis of leukotreine B5", *Tetrahedron Lett.*, **1983**, 24, 4883-4886 and Garegg, P.J., et al., "Novel reagent system for converting a hydroxy-group into an iodo-group in carbohydrates with inversion of configuration", Part 2. *J. Chem. Soc.*, **1980**, 1, 2866-2869.

The foregoing procedures preferably prepare the compound for generation of a Wittig salt. In this regard, intermolecular displacement of the iodide *via* molten triphenylphosphine (Hunig's base, 85° C) furnishes the

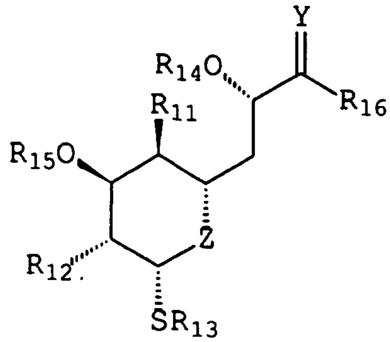
phosphonium salt **75a**, typically in high yield of about 95% for 2 steps, without involvement of the C13-C14 olefin. Thus, removal of the C14 methyl group from discodermolide significantly simplifies the generation of the requisite phosphonium salt and thereby the overall synthetic sequence.

Wittig coupling of the ylide **75a** (Figure 54) with aldehyde (-)-**67** as described in *J. Am. Chem. Soc.*, **2000**, 122 8654-8664, typically proceeds in 40% yield (7:1 *Z*:*E*) along with 35% recovery of the phosphonium salt which may be reused. Oxidative removal of the PMB moiety in **58b** (DDQ, H_2O, 97%), installation of the carbamate *via* the Kocovsky protocol, and global deprotection (3N HCI, MeOH; 89%) furnishes, for example, the C14-normethyl analog of discodermolide (+)-**I-ii**.

By way of further illustration, preferred processes according to the invention include, but are not limited to, contacting a phosphonium salt of formula I with base and an alkylthiol of formula II:

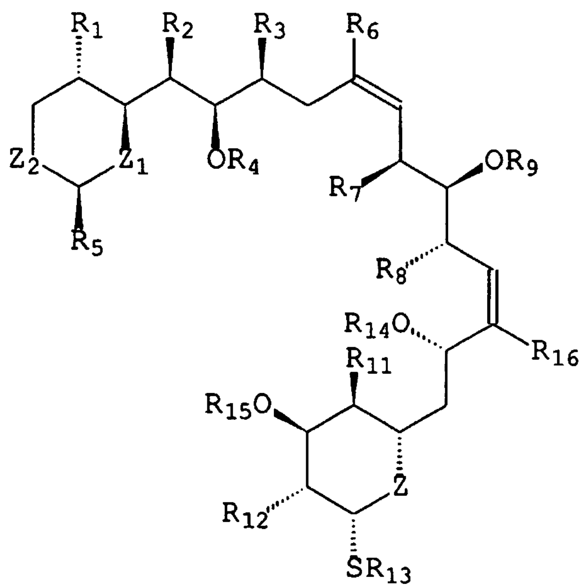


I



II

to form a diene of formula III:



III

wherein:

R_1, R_2, R_3, R_7, R_8, R_{11}, R_{12} and R_{13} are, independently, C_1-C_{10} alkyl;

X is a halogen;

R_6 is selected from the group consisting of H and C_1-C_{10} alkyl;

Z, Z_1, and Z_2 are, independently, O, S or NR';

R_4, R_9, R_{14}, and R_{15} are, independently, acid labile hydroxyl protecting groups;

R_5 is C_6-C_{14} aryl;

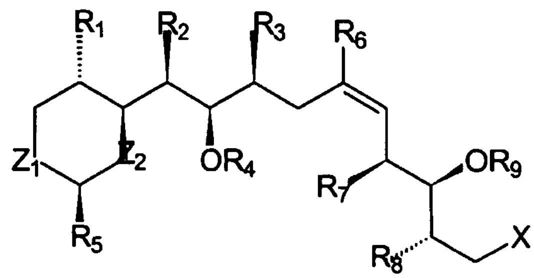
Y is O, S or NR';

R' and R_{16} are, independently, hydrogen or C_1-C_6 alkyl; and

R_{18} is C_6-C_{14} aryl.

Such procedures preferably are run in solvents such as tetrahydrofuran at -78 °C - 0 °C. Suitable bases for such procedures include sodium hexamethyldisilazide, potassium hexamethyldisilazide, and *n*-butyllithium with hexamethylphosphoramide.

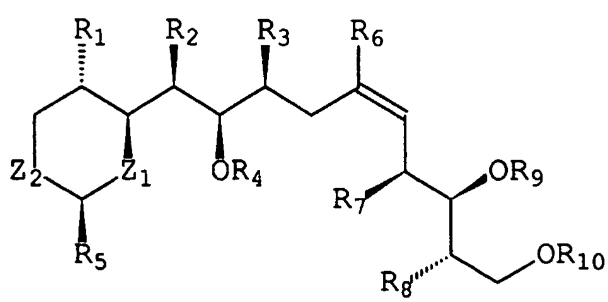
Phosphonium salts of formula I can be prepared by reacting a corresponding halogen of formula XXXXVI:



XXXXVI

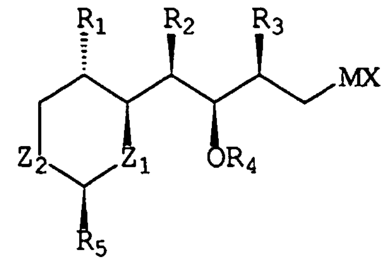
with $P(R_{18})_3$ in an for a time and under conditions effective to produce the salt. This reaction preferably is conducted in a aromatic hydrocarbon organic solvent such as toluene or benzene. A mixture of benzene and toluene in a ratio of 7:3 is preferred at a pressure of about 5 Kbar to about 20 Kbar.

The methods of the invention involve also are directed to the synthesis of alkenes of formula IV:



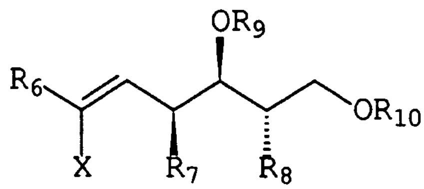
IV

by contacting organometallic reagents of formula Va:



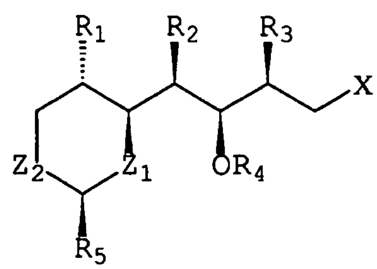
Va

with vinyl halides of formula VIa:



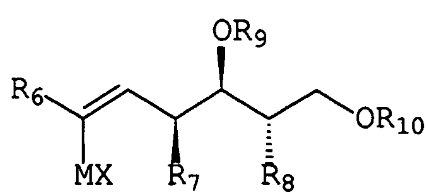
VIa

wherein M is Li, Cu, Mg, or Zn, and R_{10} is an acid stable hydroxyl protecting group. Alternatively, a vinyl halide of formula Vb:



Vb

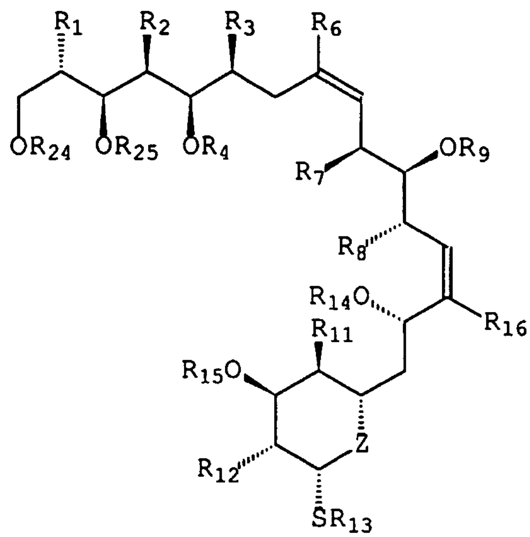
is contacted with an organometallic compound of formula VIb:



VIb

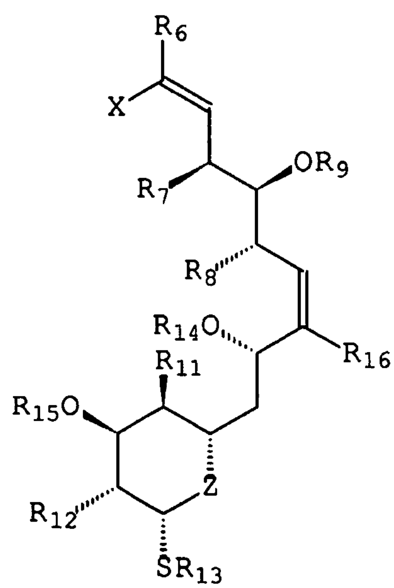
Such reactions preferably are performed in the presence of a palladium-containing catalyst such as $Pd(PPh_3)_4$, $Pd(Cl_2)(PPh_3)_2$, $Pd(Cl_2)(dppf)_2$.

In yet another aspect, the synthetic methods of the invention are directed to the preparation of compounds having formula VII:



VII

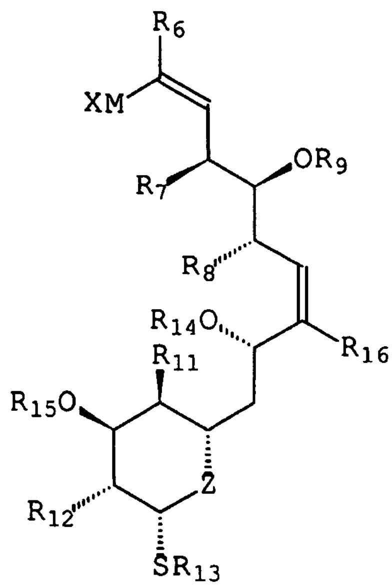
by contacting a diene of formula VIIIa:



VIIIa

with an organometallic compound having formula Va wherein R_{24} is hydrogen and R_{25} is hydrogen or an acid stable hydroxyl protecting group. Alternatively, an organometallic compound

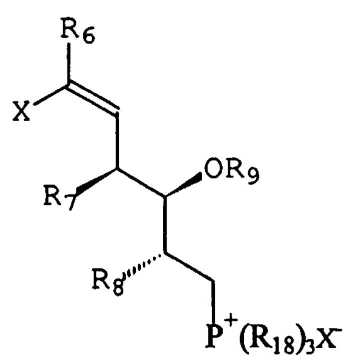
having formula VIIIb is contacted with a vinyl halide having formula Vb.



VIIIb

The reaction of compounds having formulas V and VIII preferably is performed in ether in the presence of a palladium- or nickel-containing catalyst.

The methods of the invention also involve producing dienes having formula VIIIa by contacting phosphonium salts having formula IX:

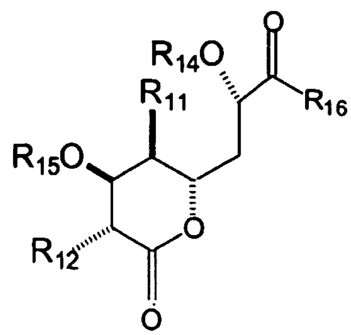


IX

with a base such as sodium hexamethyl disilazide and an alkylthiol compound having formula II. Such procedures preferably are run in solvents such as tetrahydrofuran at -78 °C - 0 °C. Suitable bases for such procedures include

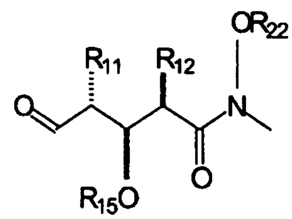
sodium hexamethyldisilazide, potassium hexamethyldisilazide, and *n*-butyllithium with hexamethylphosphoramide.

The methods of the invention also involve producing compounds of formula XXIII:



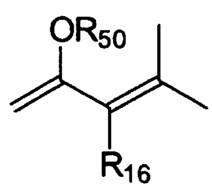
XXIII

by contacting an aldehyde of formula XXIV:



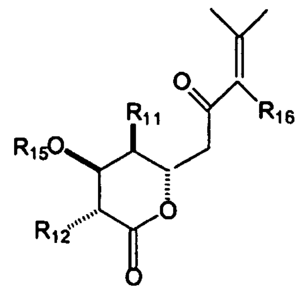
XXIV

with an enol ether of formula XXV:



XXV

in the presence of a titanium salt and an organic acid to form an enone of formula XXVI:



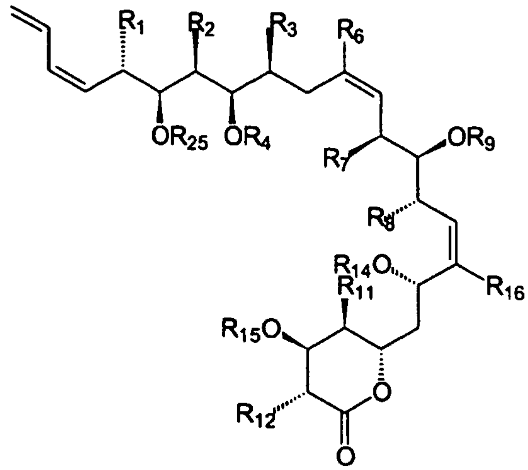
XXVI

Preferably, the reaction between aldehyde **27** and the enol ether **62** is a Mukaiyama aldol reaction wherein the Lewis acid is a titanium salt (such as $TiCl_4$) or some other Ti(IV) of Sn(IV) Lewis acid (such as $SnCl_4$) and the organic acid is trichloroacetic acid, trifluoroacetic acid, sulfuric acid, or pyridinium p-toluenesulfonate. Following the aldol reaction, enone **64** is contacted with a reducing agent to form the corresponding enol **65**. Preferably, the reducing agent is potassium tri-sec-butylborohydride or sodium tri-sec-butylborohydride (commercially available in THF as K-Selectride® and N-Selectride®, respectively) but may include chiral reducing agents such as lithium B-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride (commercially available in THF as Alpine-Hydride®.

According to the present invention, enol **65** is then contacted with a compound having formula R-L wherein R is an acid labile protecting group and L is a leaving group. Preferably, R-L is *t*-butyldimethylsilyl chloride or *t*-butyldimethysilyl triflate.

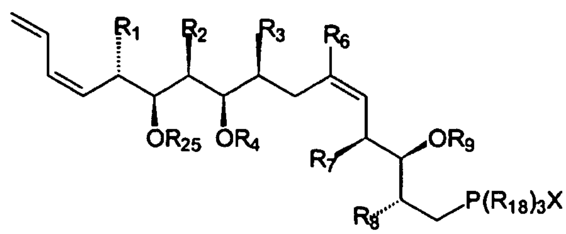
The protected enol is then oxidized with an oxidizing agent such as O_3 or the reagent combination of $NaIO_4$ with catalytic OsO_4 for a time and under conditions effective to oxidize the carbon-carbon double bond of the protected enol.

The methods of the present invention are also directed to the synthesis of diene having formula XXXIII:



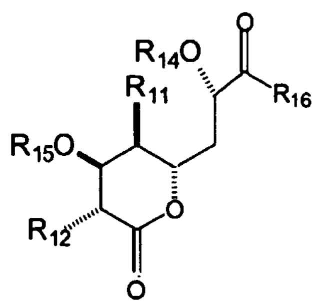
XXXIII

by contacting phosphonium salts of formula XXXIV:



XXXIV

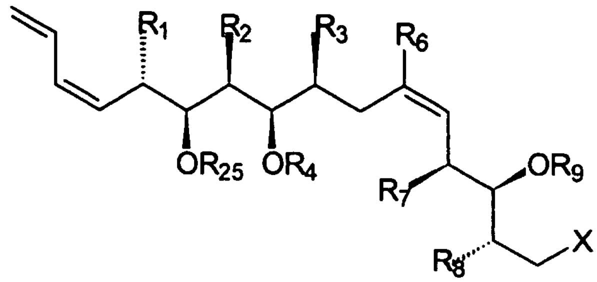
with base and a compound of formula XXXV:



XXXV

Suitable bases for such procedures include potassium hexamethyldisilazide, sodium hexamethyldisilazide, *n*-butyllithium and potassium *t*-butoxide. Preferred solvents include toluene and tetrahydrofuran, more preferably tetrahydrofuran, preferably at a temperature of -78°C-0°C.

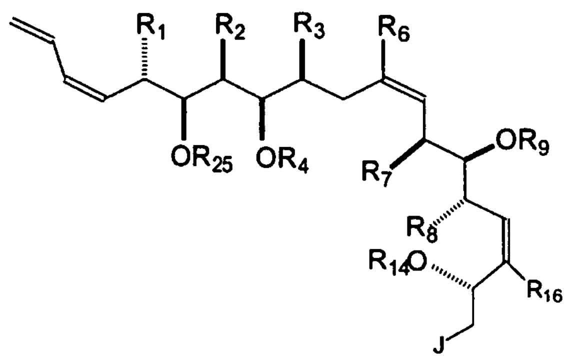
Phosphonium salts of formula XXXIV can be prepared by reacting a corresponding halogen of formula XXXXVII:



XXXXVII

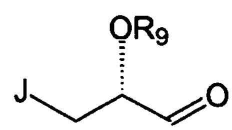
with $P(R_{18})_3$ in an for a time and under conditions effective to produce the salt. This reaction preferably is conducted in a aromatic hydrocarbon organic solvent such as toluene or benzene. A mixture of benzene and toluene in a ratio of 7:3 is preferred at a pressure of about 5 Kbar to about 20 Kbar.

Further processes of the invention involve producing compound having formula XXXVI:



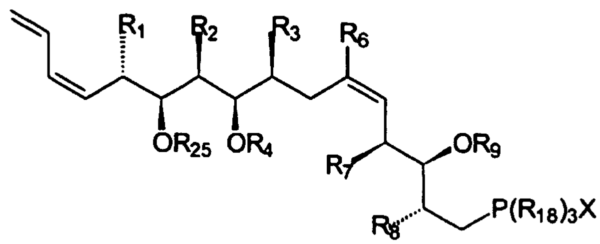
XXXVI

by contacting a compound of formula XXXVII:



XXXVII

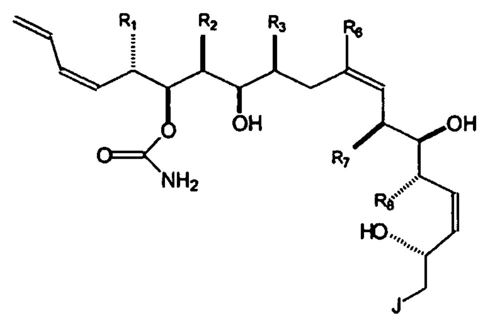
with base and a phosphonium salt of formula XXXIV:



XXXIV

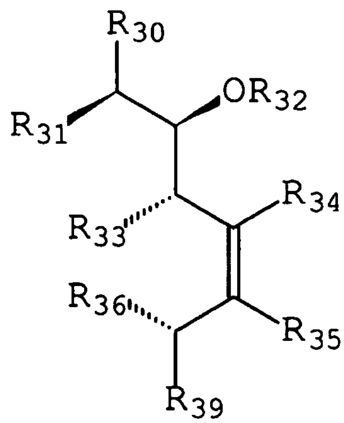
Preferred bases include sodium hexamethyldisilazide, potassium hexamethyldisilazide, *n*-butyllithium with hexamethyl-phosphoramide, and potassium *t*-butoxide. A preferred solvent is toluene, preferably at a temperature of -78°C-0°C.

According to methods of the invention, removal of the acid stable protective group and carbamate formation followed by final deprotection furnishes compounds having formula:



Although preferred synthetic methods are those directed to (+)-discodermolide and compounds having like stereochemistry, those skilled in the art will recognize that the methods disclosed herein can be readily adapted to the synthesis of antipodal compounds such as, for example, (-)-discodermolide, and *vice versa*. All such synthetic methods are within the scope of the present invention.

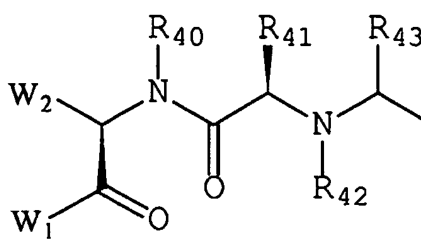
The present invention provides compounds which mimic the chemical and/or biological activity of the discodermolides. In preferred embodiments, such compounds have formula XI:



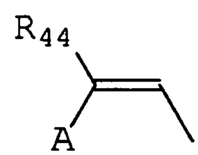
XI

where

R_{30} is substituted or unsubstituted C_1-C_{10} alkyl or a moiety formula XII or XIII:

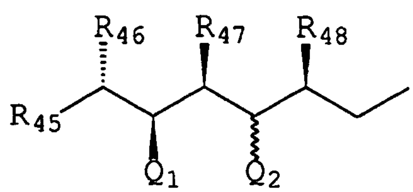


XII



XIII

where A is C_1-C_{20} alkyl, $-CH_2NH(T)$ or a moiety of formula XIV:



XIV

wherein

T is peptide having 1 to about 10 amino acids;

R_{32}, R_{40}, R_{42}, R_{43}, R_{46}, R_{47}, and R_{48} are, independently, hydrogen or C_1-C_6 alkyl;

R_{41} is a side chain of an amino acid;

W_1 and W_2 are, independently, $-OR_{49}$ or $-NHP_1$;

P_1 is hydrogen or an amine protecting group;

R_{33} and R_{36} are, independently, hydrogen, C_1-C_{10} alkyl, -OR_{50}, =O or together form -CH_2-CH_2-;

R_{34} and R_{35} are, independently, hydrogen or together form -C(H)=C(H)-C(H)=C(H)-;

R_{39} is -OR_{51} or -CH_2-R_{51};

R_{31} and R_{44} are, independently, C_1-C_{10} alkyl;

Q_1 and Q_2 are, independently, hydrogen, -OR_Q, -NHR_{52}, -OC(=O)NH_2 or together form -O-C(O)-NH-;

R_Q is hydrogen or a hydroxyl protecting group;

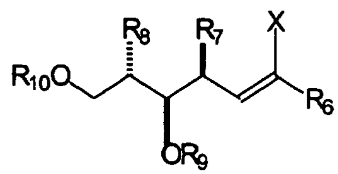
R_{51} is substituted or unsubstituted C_6-C_{14} aryl, tetrahydropyranyl, furanosyl, pyranosyl, C_3-C_{10} lactonyl or 2-pyranonyl;

R_{45} is C_1-C_6 alkenyl, C_1-C_6 alkyl, C_6-C_{14} aryl, C_2-C_{10} heterocycloalkyl, C_3-C_{10} cycloalkyl, or C_7-C_{15} aralkyl; and

R_{49}, R_{50}, and R_{52} are, independently, hydrogen or C_1-C_6 alkyl.

Some preferred compounds having formula XI are shown in Figures 33-36.

In other aspects, the present invention provides a process for forming a halogenated olefin of formula:



wherein:

R_6 is selected from H and C_1-C_6 alkyl;

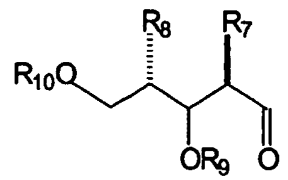
R_7 and R_8 are independently C_1-C_{10} alkyl;

R_9 is an acid labile hydroxyl protecting group;

R_{10} is an oxidatively labile protecting group; and,

X is halogen;

the process comprising contacting an aldehyde of formula:

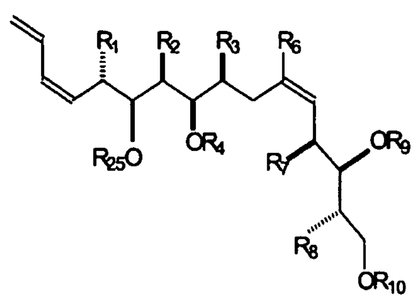


with a compound of formula $(R_{18})_3$ $PCHXR_6$ in the presence of base, wherein R_{18} is C_6-C_{14} aryl, for a time and conditions effective to form the halogenated olefin.

Preferred conditions include cooling a suspension of R_6Ph_3PX in an aprotic solvent, such as tetrahydrofuran, at about 0 °C to -25 °C, and contacting the suspension with a strong base such as an alkyl metal. Suitable strong bases include, but are not limited to alkyl lithiums, such as butyl lithium, t-butyl lithium, and the like. The solution may be added to a precooled solution of X_2, preferably at a rate such that the temperature of the resultant solution does not exceed -70 °C. An additional base, such as sodium hexamethyl disilazide, is preferably added over approximately a 10 to 60 minute period followed by introduction of the aldehyde.

In certain preferred embodiments, R_6, R_7, and R_8 are independently C_1-C_4 alkyl, and R_{18} is phenyl. In certain more preferred embodiments, R_6, R_7, and R_8 are methyl, X is iodine, R_2 is tert-butyldimethylsilyl, and R_{10} is paramethoxybenzyl.

The present invention also provides process for forming a triene of formula:



wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

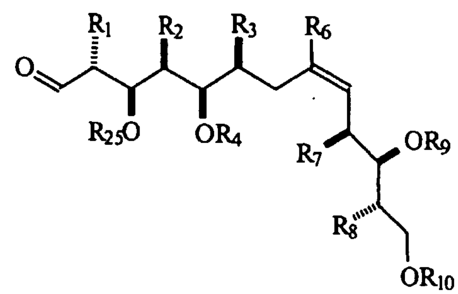
R_3 and R_6 are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are independently acid labile hydroxyl protecting groups;

R_{25} is an oxidatively labile hydroxyl protecting group; and;

R_{10} is a hydroxy protecting group;

the process comprising contacting an aldehyde of formula:

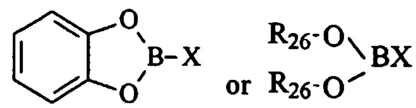


with a compound of formula $Ph_2PCH_2CH{=}CH_2$ in the presence of a base and a compound of formula $Ti(O\text{-}R_{27})_4$, wherein R_{27} is C_{1-6} alkyl; followed by treatment with $R_{28}X$ wherein R_{28} is C_{1-6} alkyl and X is a halogen, for a time and under conditions effective to form the triene.

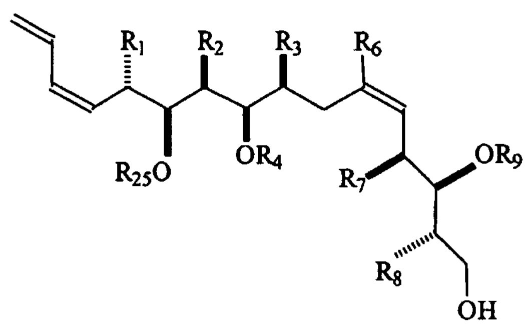
Preferable conditions include precooling a solution of $Ph_2PCH_2CH{=}CH_2$ in an aprotic solvent, such as tetrahydrofuran, to a temperature of below 0 °C, more preferably below -70 °C, followed by the addition over a suitable time period of a strong base such as an alkyl metal. Strong bases may include, but are not limited to alkyl lithiums, such as butyl lithium, t-butyl lithium, and the like. The solution is preferably treated with $Ti(O\text{-}R_{27})_4$ and stirred for a suitable period, followed by the introduction of the aldehyde. An excess of $R_{28}X$ is then added and the solution warmed over a suitable time period to afford the triene.

In certain preferred embodiments, R_1, R_2, R_7, and R_8 are independently C_1-C_4 alkyl; R_{10} is selected from triphenyl methyl, dimethoxyl benzyl, and dimethoxybenzyl-O-methyl; the base is C_1-C_6 alkyl lithium; R_{27} is isopropyl, R_{28} is methyl; and X is iodine.

In another embodiment, the process for forming the triene further comprising contacting the triene with a borane compound of formula:

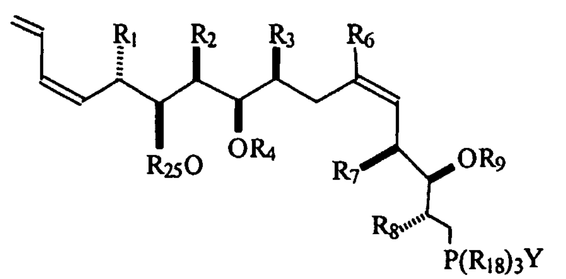


wherein X is a first halogen and R_{26} is selected from C_{6-14} aryl and C_{1-6} alkyl, to form a triene alcohol of formula:



and;

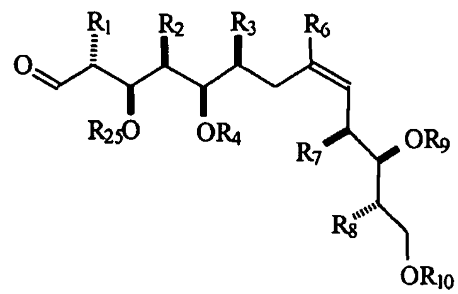
contacting the triene alcohol with a halogen such as iodine in the presence of base and $P(R_{18})_3$ to form the corresponding iodide, followed by further treatment of the resulting iodide with Hunig's base and $P(R_{18})_3$ under conditions to form a phosphonium salt of formula:



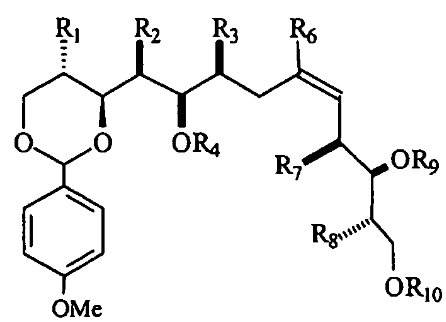
Preferable conditions include adding a protic solvent to a solution of the borane and a polar solvent. Preferable protic solvent include, but are not limited to, alcoholic solvents such as methanol. Preferable polar solvents include, but are not limited to, chlorinated solvents. The solution may be added over a suitable period

of time to a solution of trityl ether to provide the triene alcohol. The triene alcohol is preferably stirred in a solution of $P(R_{18})_3$ and a base, to which Y_2 is added. In certain embodiments, R_{18} is phenyl, the base is imidazole and Y_2 is iodine. The resultant compound is preferably stirred in a solution to which an amine base, such as Hunig's base, is added followed by $P(R_{18})_3$. The resultant solution may be subjected to elevated pressure for a period of time sufficient to form the phosphonium salt.

In certain embodiments, the aldehyde of formula:



is formed by a process comprising contacting a compound of formula:



wherein:

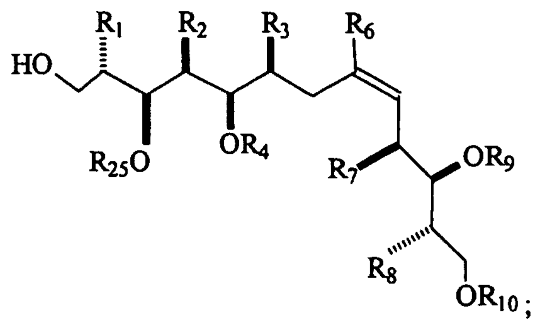
R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

R_3 and R_6 are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are independently acid labile hydroxyl protecting groups; and

R_{10} is a trityl group;

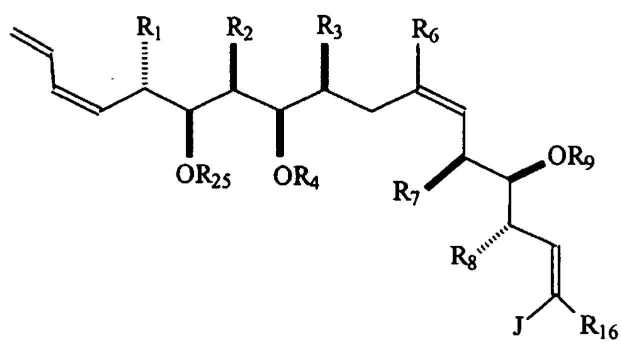
with hydride to form an alcohol of formula:



and oxidizing the alcohol to form the aldehyde.

The formation of the alcohol as well as the oxidation may be performed, for example, at reduced temperatures such as about 0 °C or lower. In certain embodiments, the hydride is diisobutylaluminum hydride (DIBAL-H) and the oxidation is accomplished through treatment of the alcohol with Dess-Martin periodinane.

The present invention further provides a process for forming a tetraene of formula:



wherein:

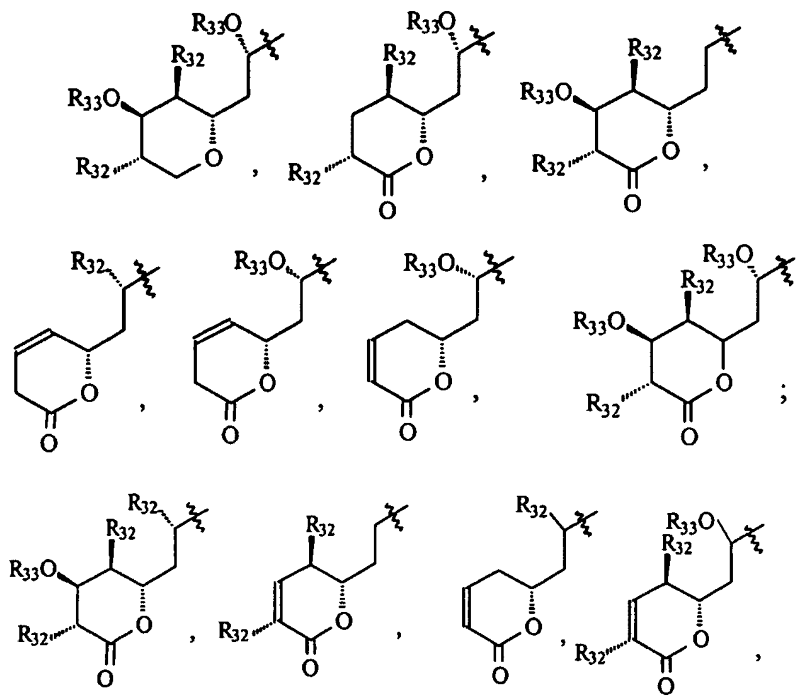
R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

R_3, R_6, and R_{16} are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are independently an acid labile hydroxyl protecting group;

R_{25} is an acid stable hydroxyl protecting group; and

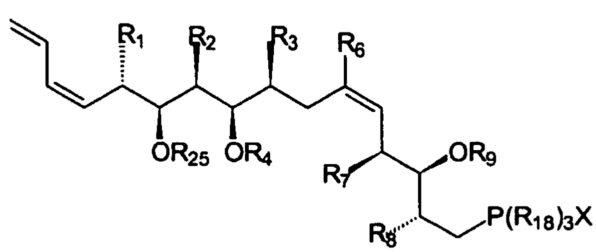
J is selected from:



alkaryl, and alkheteroaryl;
wherein R_{32} is H or C_1-C_6 alkyl and R_{33} is H or an acid labile hydroxyl protecting group;
the process comprising contacting a compound of the formula:

J-CHO

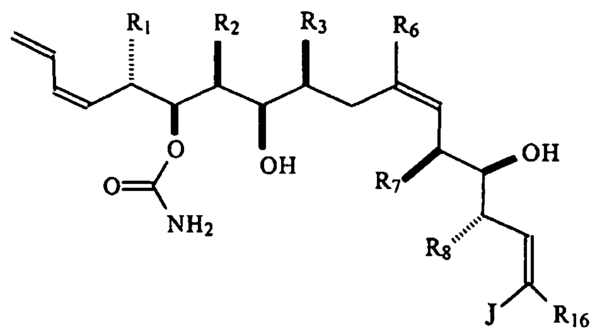
with a phosphonium salt of the formula:



wherein R_{18} is C_6-C_{14} aryl, in the presence of a base for a time and under conditions effective to form the tetraene. In certain preferred embodiments, the process according to

claim 11 wherein R_1, R_2, R_7, and R_8 are independently C_1-C_4 alkyl, R_3 and R_6 are independently selected from hydrogen and C_1-C_4 alkyl, and R_{32} is C_{1-4} alkyl.

The present invention also provides a process for forming a tetraene of formula:

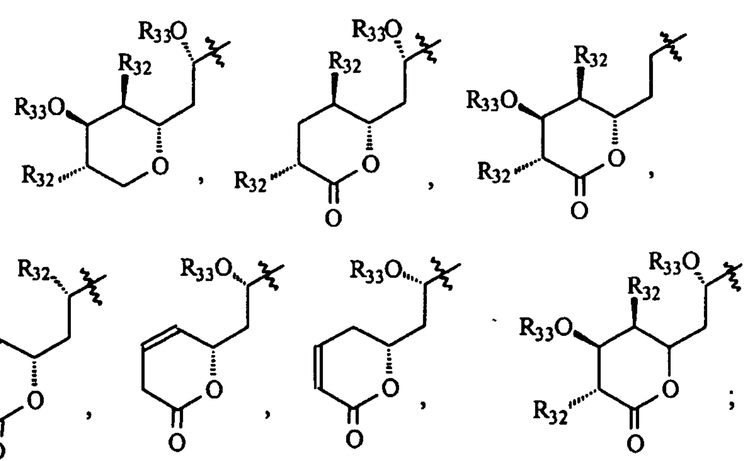


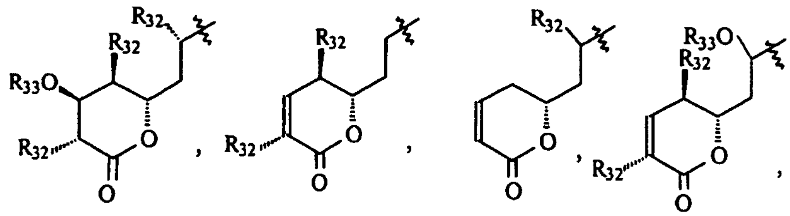
wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

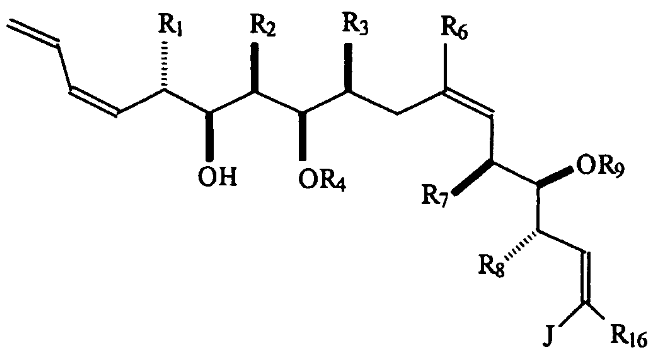
R_3, R_6, and R_{16} are independently selected from hydrogen and C_1-C_6 alkyl; and

J is selected from:





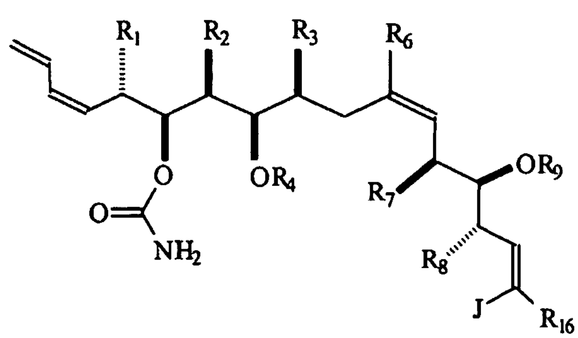
alkaryl, and alkheteroaryl;
wherein R_{32} is H or C_1-C_6 alkyl and R_{33} is H;
the process comprising contacting an alcohol of formula:



wherein R_4, R_9, and R_{33} are acid labile hydroxyl protecting groups, with an isocyanate of the formula:

$$X_3CC(=O)NCO$$

wherein X is a halogen, to form a carbamate intermediate; contacting the carbamate intermediate with neutral alumina to form a carbamate of formula:

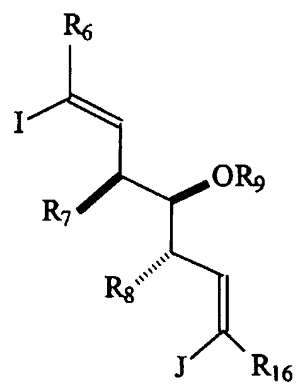


and;

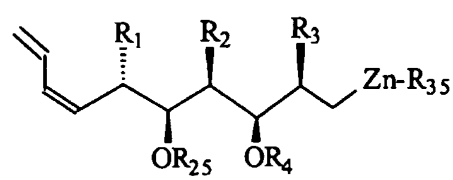
removing the acid labile hydroxyl protecting groups by contacting the carbamate with acid in a protic solvent to form the tetraene.

A solution of the alcohol in a polar solvent may be contacted with the isocyanate at room temperature for a period of about 15 to 45 minutes followed by loading the solution directly onto neutral alumina. After a suitable period of time, for example, several hours, the material may be flushed from the column with an suitable solvent system. In certain preferred embodiments, the acid labile protecting group is removed with aqueous hydrochloric acid in an alcoholic solvent. More preferably, the addition of acid is performed in portions and over a period of time which minimizes precipitation.

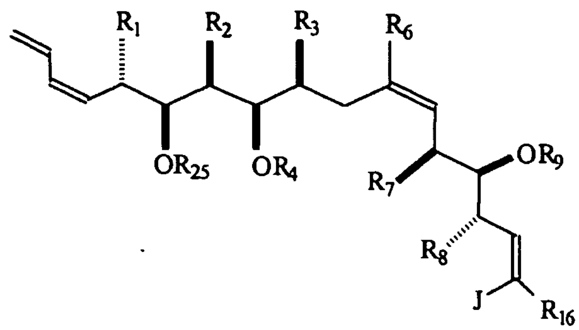
In certain preferred embodiments, the alcohol is formed by contacting a compound of formula:



with a compound of formula:

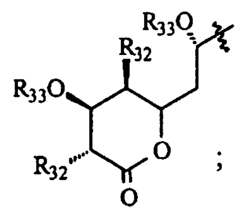


wherein R_{25} is an oxidatively labile protecting hydroxyl protecting group, and R_{35} is selected from C_1-C_4 alkyl and a halogen, in the presence of a metal coupling catalyst for a time and under conditions effective to form a coupling product of formula:

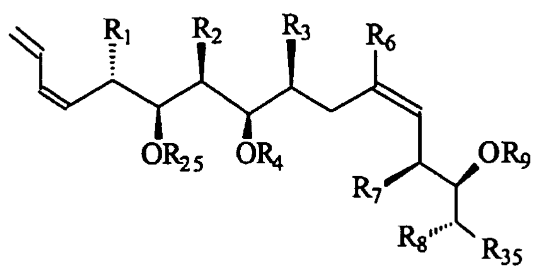


and deprotecting the coupling product to form the alcohol.

In certain preferred embodiments, R_1, R_2, R_7, and R_8 are independently C_1-C_4 alkyl, R_3, R_6, and R_{16} are independently hydrogen or C_1-C_4 alkyl, J is:



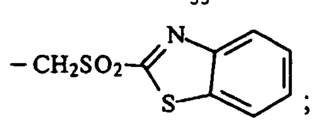
the isocyanate is $Cl_3CC(=O)NCO$, the acid is HCl, and the polar solvent is an alcohol selected from methanol, ethanol, and isopropanol. In other preferred embodiments, the alcohol is formed by contacting a compound of formula:



wherein:

R_{25} is an oxidatively labile protecting group;

R_{35} is selected from $CH_2P(=O)Ph_2$ and

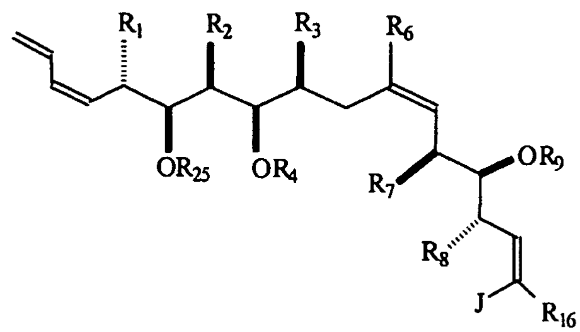


X is a halogen; and

R_{18} is C_{6-14} aryl;

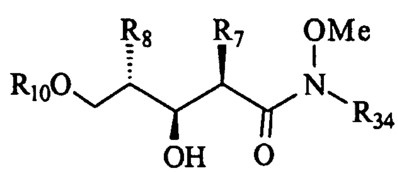
with a compound of formula: J-C(O)R^{16};

in the presence of a base to form a coupling product of formula:



and deprotecting the coupling product (removing R_{25}) to form the alcohol. In certain more preferred embodiments, the protic solvent is an alcohol selected from methanol, ethanol, and isopropanol.

In other embodiments, the present invention provides a process for forming an alcohol of formula:



wherein:

R_7 and R_8 are independently C_1-C_{10} alkyl;

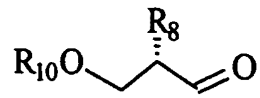
R_{10} is an acid stable hydroxyl protecting group;

R_{34} is selected from $(CH_2)_nC_6$-C_{14} aryl and $(CH_2OCH_2)C_6$-C_{14} aryl, wherein the aryl is substituted with 0-3 R_{35};

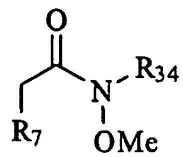
R_{35} is selected from F, CF_3, Br, Cl, and NO_2; and

n is selected from 0 and 1;

the process comprising contacting a compound of formula:

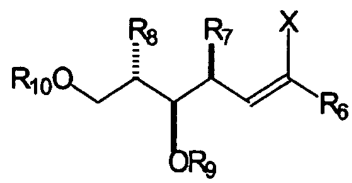


with the enolate of a compound of formula:



in the presence of Lewis acid for a time and under conditions effective to form the alcohol.

The present invention also provides a compound of formula:



wherein:

R_6 is C_1-C_4 alkyl;

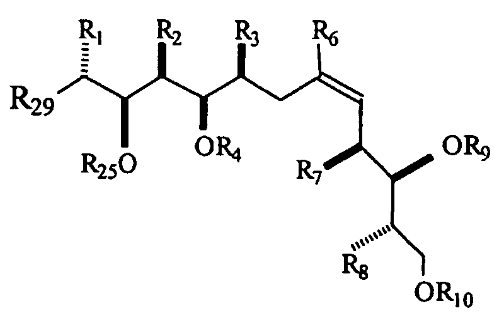
R_7 and R_8 are independently C_1-C_{10} alkyl;

R_9 is an acid labile hydroxyl protecting group;

R_{10} is an acid stable hydroxyl protecting group; and

X is halogen.

The present invention also provides a compound of formula:



wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

R_3 and R_6 are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are independently acid labile hydroxyl protecting groups;

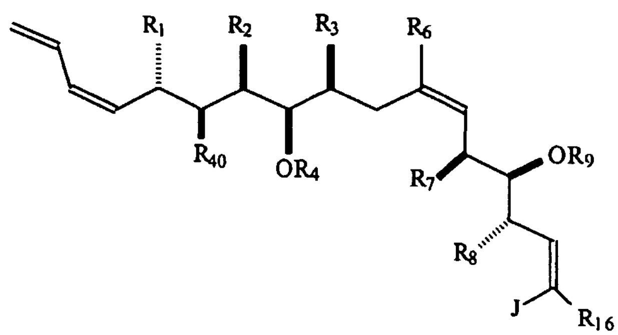
R_{25} is an oxidatively labile hydroxyl protecting group; and

R_{10} is a trityl group; and

R_{29} is selected from OH, CHO, and -CH=CH-CH=CH_2.

In certain preferred compounds, R_1, R_2, R_7, and R_8 are methyl, and R_3 and R_6 are independently selected from hydrogen and methyl.

In other embodiments, the present invention provides a compound of formula:



wherein:

R_1, R_2, R_7, and R_8 are independently C_1-C_{10} alkyl;

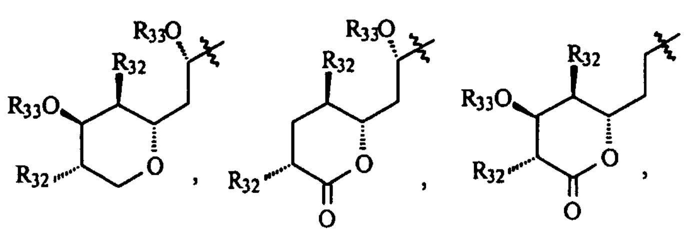
R_3, R_6, and R_{16} are independently selected from hydrogen and C_1-C_6 alkyl;

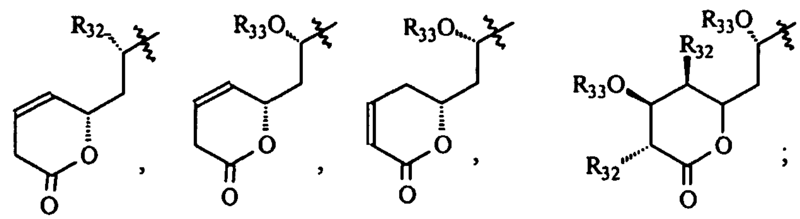
R_4, R_9, and R_{14} are acid labile protecting groups;

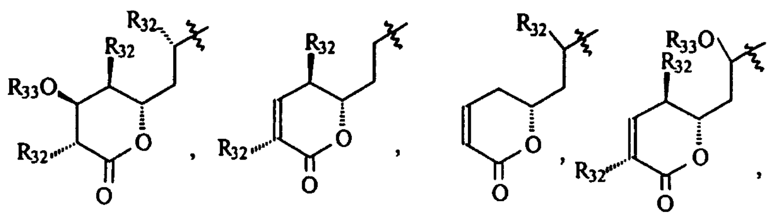
R_{40} is selected from OR_{25} and OC(=O)NH_2;

R_{25} is an acid stable protecting group; and

J is selected from:

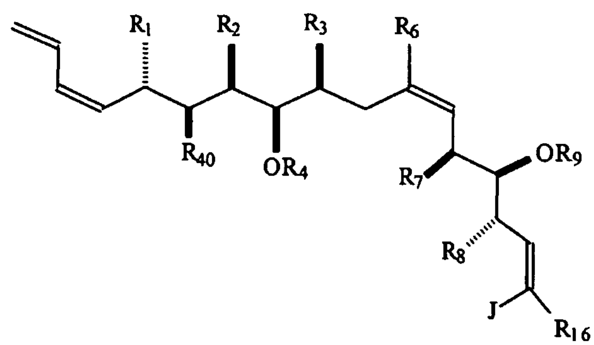






wherein R_{32} is C_1-C_6 alkyl and R_{33} is selected from H and an acid labile hydroxy protecting group.

The present invention also provides a compound of formula:



wherein:

R_1, R_2, R_7, and R_8 are independently selected from hydrogen and C_1-C_{10} alkyl;

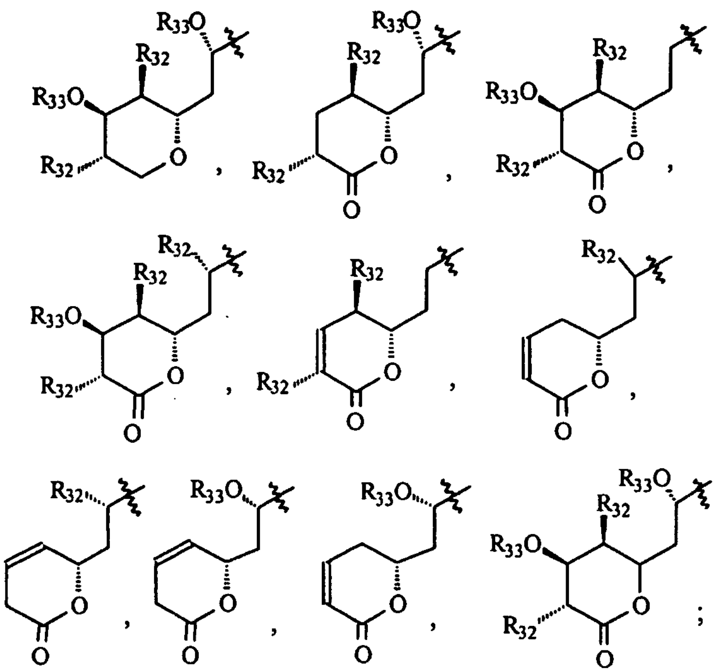
R_3, R_6, and R_{16} are independently selected from hydrogen and C_1-C_6 alkyl;

R_4 and R_9 are selected from hydrogen and acid labile protecting groups;

R_{40} is selected from OR_{25} and $OC(=O)NH_2$;

R_{25} is selected from hydrogen and an oxidatively labile protecting group; and

J is selected from:



alkaryl and alkheteroaryl wherein aryl and heteroaryl are optionally substituted and alk is optionally substituted with R_{32} or OR_{33};

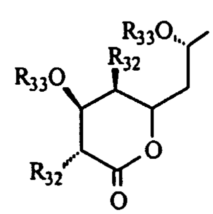
wherein:

R_{32} is selected from hydrogen and C_1-C_6 alkyl; and

R_{33} is selected from hydrogen and an acid labile hydroxy protecting group. In certain embodiments, R^6 is H.

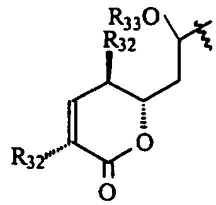
In certain preferred embodiments, R_6 is H, R_1, R_2, R_7,

and R_8 are methyl, R_4, $R_{9,}$ and R_{33} are hydrogen. In other preferred embodiments, the compound of claim 1 wherein R_1, R_2, R_7, and R_8 are methyl; R_4, R_6, and R_9 are hydrogen; and R_{40} is $-OC(O)NH_2$. In other preferred embodiments, J is



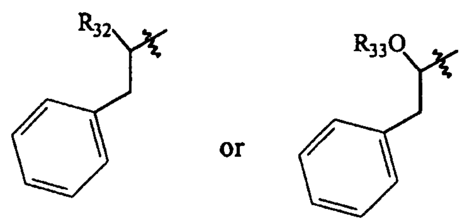
wherein R_{32} is methyl and R_{33} is hydrogen.

In other preferred embodiments, R_1, R_2, R_6, R_7, and R_8 are methyl; R_4 and R_9 are H; R_{40} is $-OC(O)NH_2$; and J is



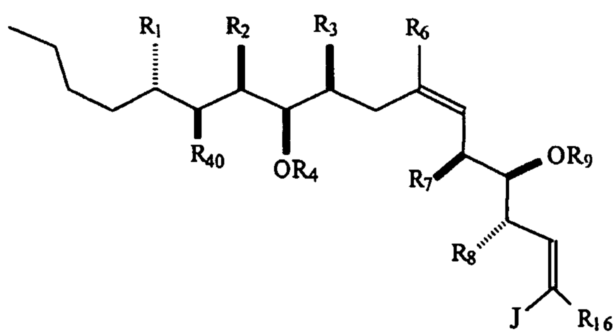
wherein R_{32} is methyl and R_{33} is H.

In other preferred embodiments, J is



wherein the phenyl group is optionally substituted with C_1-C_4 alkyl, haloalkyl, hydroxy, alkoxy, or haloalkoxy. In other preferred embodiments, the phenyl is substituted with OH.

In certain preferred embodiments, the present invention provides a compound having the following formula:



wherein:

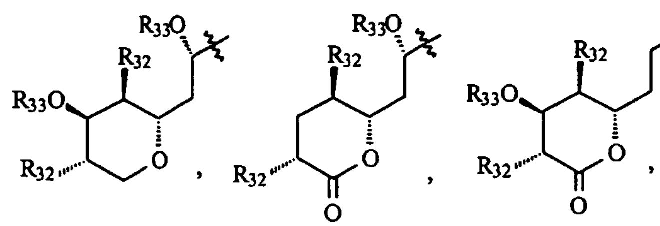
R_1, R_2, R_7, and R_8 are independently hydrogen or C_1-C_{10} alkyl;

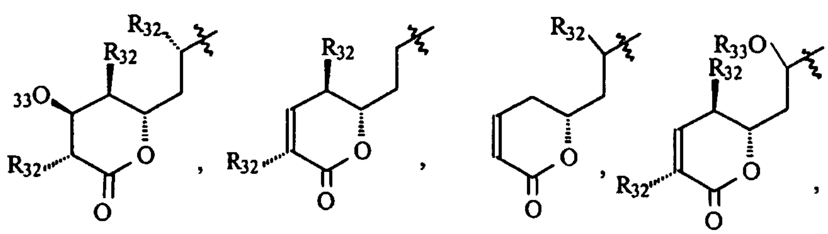
R_3, R_6, and R_{16} are independently hydrogen or C_1-C_6 alkyl;

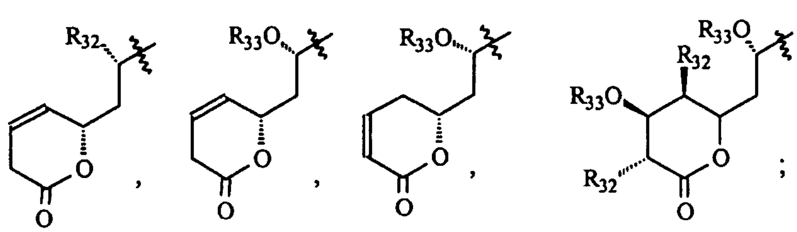
R_4, and R_9 are independently hydrogen or acid labile protecting groups;

R_{40} is selected from OR_{25} and $OC(=O)NH_2$;

R_{25} is hydrogen or an oxidatively labile protecting group; and J is selected from:







alkaryl and alkheteroaryl wherein aryl and heteroaryl are optionally substituted and alk is optionally substituted with R_{32} or OR_{33};

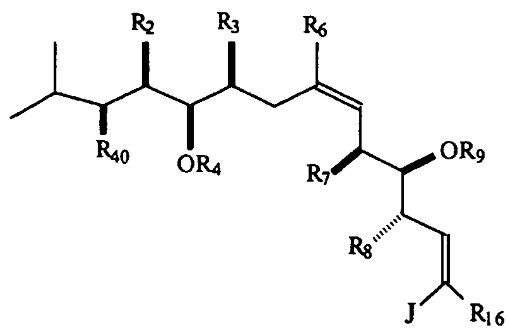
wherein

R_{32} is hydrogen or C_1-C_6 alkyl; and

R_{33} is hydrogen or an acid labile hydroxy protecting group. In certain preferred embodiments, R_6 is H. In other

embodiments, R_1, R_2, R_7, and R_8 are methyl. In other embodiments, R_4, R_9, and R_{33} are hydrogen. In other embodiments, R_1, R_2, R_7, and R_8 are methyl; R_4, R_6, R_9, and R_{33} are H; and R_{40} is $-OC(O)NH_2$.

In certain embodiments, the present invention provides a compounds having the formula:



wherein

R_2, R_7, and R_8 are independently hydrogen or C_1-C_{10} alkyl;

R_3, R_6, and R_{16} are independently hydrogen or C_1-C_6 alkyl;

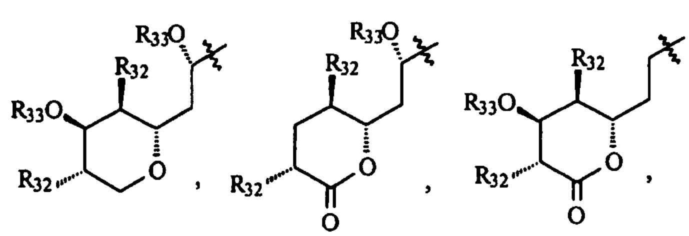
R_4, R_9, and R_{33} are independently hydrogen or acid labile protecting groups;

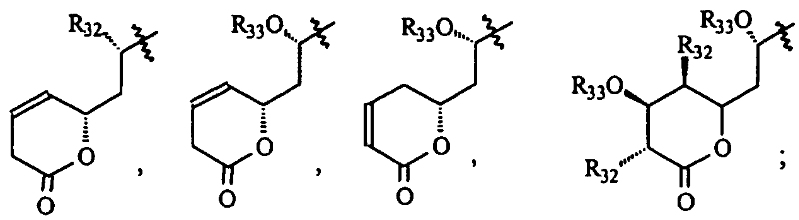
R_4 and R_9 are independently hydrogen or acid labile protecting hydroxl groups;

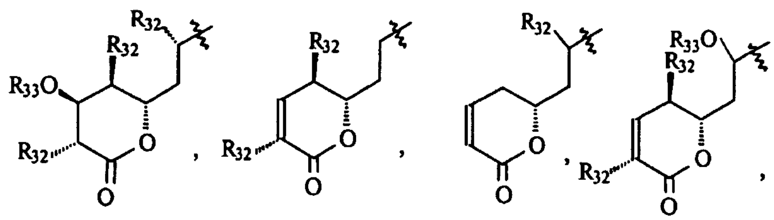
R_{40} is selected from OR_{25} and $OC(=O)NH_2$;

R_{25} is hydrogen or an oxidatively labile protecting group; and

J is selected from:







alkaryl and alkheteroaryl wherein aryl and heteroaryl are optionally substituted and alk is optionally substituted with R_{32} or OR_{33};

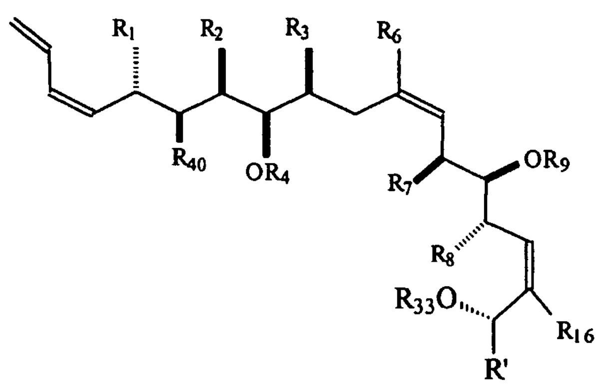
wherein

R_{32} is hydrogen or C_1-C_6 alkyl; and

R_{33} is hydrogen or an acid labile hydroxy protecting group.

In certain preferred embodiments, R_6 is H. In other embodiments, R_1, R_2, R_7, and R_8 are methyl.

In certain embodiments, the present invention provides a compound having the formula:



wherein:

R_1, R_2, R_7, and R_8 are independently hydrogen or C_1-C_{10} alkyl;

R_3, R_6, and R_{16} are independently hydrogen or C_1-C_6 alkyl;

R_4, R_9, and R_{33} are independently hydrogen or acid labile protecting groups;

R_4, R_9, are independently hydrogen or acid labile protecting hydroxl groups;

R_{25} is hydrogen or an oxidatively labile protecting group;

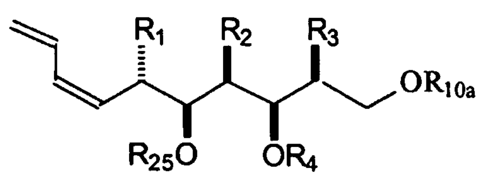
R_{40} is selected from OR_{25} and $OC(=O)NH_2$; and

R' is methyl or alkyl-R";

R" is C_1-C_{10} alkoxy, hydroxy, or $-C(O)CH_3$.

In certain preferred embodiments, R_6 is hydrogen. In other embodiments, R_1, R_2, R_7, and R_8 are methyl. In other embodiments, R_4, R_9, and R_{33} are H. In other embodiments, R_1, R_2, R_7,and R_8 are methyl; R_4, R_6, R_9, and R_{33} are H; and R_{40} is $-OC(O)NH_2$.

The present invention also provides process for forming a diene of formula:



wherein:

R_1 and R_2 are independently C_1-C_{10} alkyl;

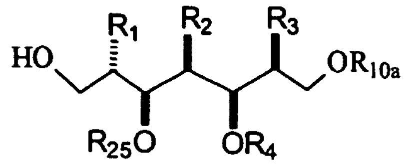
R_3 is selected from hydrogen and C_1-C_6 alkyl;

R_4 is an acid labile hydroxyl protecting group;

R_{25} is an oxidatively labile hydroxyl protecting group; and;

R_{10a} is a hydroxyl protecting group or an oxazolidinone;

the process comprising contacting an alcohol of formula:

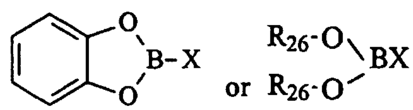


with an oxidizing agent, such as Dess-Martin periodinane, followed by a compound of formula $Ph_2PCH_2CH=CH_2$ in the presence of a base and a compound of formula $Ti(O\text{-}R_{27})_4$, wherein R_{27} is C_{1-6} alkyl; followed by treatment with $R_{28}X$ wherein R_{28} is C_{1-6} alkyl and X is a halogen, for a time and under conditions effective to form the diene. Alternatively, a compound of formula $Ph_2PCH=CH_2CH_2Ti(O\text{-}R_{27})_4$ may be preformed and added to the oxidized alcohol under similar conditions.

By way of illustration, preferable conditions include precooling a solution of $Ph_2PCH_2CH=CH_2$ in an aprotic solvent, such as tetrahydrofuran, to a temperature of below 0 °C, more preferably below -70 °C, followed by the addition over a suitable time period of a strong base such as an alkyl metal. Strong bases may include, but are not limited to alkyl lithiums, such as butyl lithium, t-butyl lithium, and the like. The solution is preferably treated with $Ti(O\text{-}R_{27})_4$ and stirred for a suitable period, followed by the introduction of the aldehyde. An excess of $R_{28}X$ is then added and the solution warmed over a suitable time period to afford the diene.

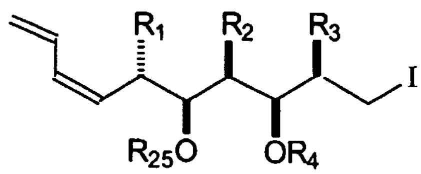
In certain preferred embodiments, R_1, R_2, R_7, and R_8 are independently C_1-C_4 alkyl; R_{10} is selected from triphenyl methyl, dimethoxyl benzyl, and dimethoxybenzyl-O-methyl; the base is C_1-C_6 alkyl lithium; R_{27} is isopropyl, R_{28} is methyl; and X is iodine.

In another embodiment, when R_{10a} is a hydroxyl protecting group, the process further comprises contacting the diene with a borane compound of formula:



wherein X is a first halogen and R_{26} is selected from C_{6-14} aryl and C_{1-6} alkyl, and;

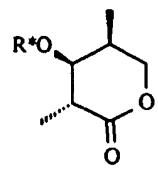
contacting the diene alcohol with a halogen such as iodine in the presence of $P(R_{18})_3$ to form the corresponding halogenated diene of formula:



Preferable conditions include adding a protic solvent to a solution of the borane and a polar solvent. Preferable protic solvent include, but are not limited to, alcoholic solvents such as methanol. Preferable polar solvents include, but are not limited to, chlorinated solvents. The solution may be added over a suitable period of time to a solution of trityl ether to provide the diene alcohol. The diene alcohol is preferably stirred in a solution of $P(R_{18})_3$ to which Y_2 is added. In certain embodiments, R_{18} is phenyl and Y_2 is iodine.

In another embodiment, when R_{10a} is an oxazolidinone, the process further comprises contacting the diene with $LiBH_4$ followed by a halogen, such as iodine, in the presence of $P(R_{18})_3$ to form the corresponding halogenated diene.

Intermediates which may be useful for the preparation of the compounds described herein, particularly the δ-lactone ring of discodermolide analogs, include the structure:



wherein R^* is hydrogen or a protecting group.

Cell Culture

The A549 lung carcinoma cell line was maintained as described in Kavallaris, M., et al., "Taxol-resistant epithelial ovarian tumors are associated with altered expression of specific β-tubulin isotypes", *J Clin. Invest.*, **1997**, 100, 1282-1293.

The SKOV3 ovarian carcinoma cell line was obtained from Dr. V. Ling and was maintained as described in McDaid, H.M., et al., "Structure-activity profiles of eleutherobin analogs and their cross-resistance in Taxol-resistant cell lines", *Cancer Chemother. Pharmacol.*, **1999**, 44, 131-137.

***In Vitro* Tubulin Polymerization Assay**

Microtubule polymerization was evaluated by recording the change in turbidity of MTP at 350 nm for 100 min in a spectrophotometer (UVIKON, Research Instruments Int., San Diego, CA). *See*, for example, Shelanski, M.L., et al., "Microtuble assembly in the absence of added nucleotides", *Proc. Natl. Acad. Sci. USA*, **1973**, 70, 765-768. Purified MTP was diluted in assembly buffer containing 0.1 M MES, I mM EGTA, 0.5 mM $MgCl_2$, and 3 M glycerol (pH 6.6) to a final concentration of 1 mg/ml. All compounds were evaluated at a concentration of 10 μM at 37°C in the absence of GTP. The changes in absorption that occurred during the first 5 min were used to plot initial slopes from the linear portion of each curve in order to compare the initial activity of each compound.

The activities of Taxol, (+)-discodermolide, and

several structural analogs were determined in the foregoing *in vitro* tubulin polymerization assay that measures changes in absorbance that correlate with the extent of microtubule polymerization. It will be appreciated that microtubule polymerization involves both nucleation (initiation) and elongation steps. The initial rates of polymerization reflect the nucleation process. *See*, for example, Gaskin, F., et al. "Turbidimetric studies of the in vitro assembly and disassembly of porcine neurotubules", *J. Mol. Biol.*, **1974**, 89, 737-758. Taxol, (+)-discodermolide, and the four analogs I-i, I-ii, I-iii, and I-iv (Figure 57), all induced tubutin assembly in the absence of GTP that is nomally required for microtuble assembly (Figure 59). The microtubles formed in the presence of Taxol, (+)-discodermolide, and these four analogs were all stable against calcium-induced depolymerzation.

With reference to Figure 59, the extent of polymerization for (+)-discodermolide, analogs I-i and I-ii, and Taxol were essentially the same after 100 min (Figure 59, curves 1-4). Analogs I-iii and I-iv demonstrated reduced polymerization, attaining approximately 50% of the level of polymerization observed with (+)-discodermolide (Figure 59, curves 5,6). The proportion of polymerized tubulin for each compound also was determined by removing 200 μL aliquots at the end of the assay, centrifuging at 100,000 g for 30 min, and measuring the protein content in the supernatant. By this method, the level of polymerization induced by (+)-discodermolide and analogs I-i and I-ii was comparable, whereas analogs I-iii and I-iv had approximately 50% more protein in the supernatant and hence less polymer in the precipitate.

The initial slopes (0-5 min) are presented in the inset in Figure 59. The slope for (+)-discodermolide (curve 1) was assigned a value of 1.0 to which the slopes for the other compounds were compared. The structural analogs (curves 3-6) gave values of 0.26, 0.39, 0.08, and 0. 14,

respectively; Taxol had a value of 0.28 (curve 2). This data reflects the potent nucleating activity of (+)-discodermolide and its derivatives.

Electron Microscopy

Aliquots (50μL) were taken from the *in vitro* polymerization assay at the end of the reaction and placed onto 300-mesh carbon-coated, Formavar-treated copper grids. Samples were then stained with 20 μL of 2% uranyl acetate and viewed with a JEOL model 100CX electron microscope. To determine the lengths of the microtubules, electron micrograph negatives were scanned and then analyzed using IP Lab software. Measurements were performed on negatives at x 10000 and x50000, with a minimum of 50 microtubules measured for each compound.

The microtubule protein from each *in vitro* assay was examined by electron microscopy to confirm that normal microtubules were formed in the presence of the compounds. In all cases, except for the DMSO control, microtubules were observed. As reported in Kowalski, R.J., et al., "The microtuble-stabilizing agent discodermolide competitively inhibits the binding of Paclitaxel (Taxol) to tubulin polymers, enhances tubulin nucleation reactions more potently than Paclitaxel, and inhibits the growth of Paclitaxel-resistant cells", *Mol. Pharmacol.*, **1997**, 52, 613-622, (+)-discodermolide produced much shorter microtubules than those formed in the presence of GTP or Taxol, emphasizing the major effect that (+)-discodermolide has on microtubule nucleation. Table 1 provides a comparison of microtubule lengths after assembly with Taxol, discodermolide and analogs I-i, I-ii, I-iii, and I-iv.

Table 1

Compound	Average Polymer Length (μm)
Taxol	3.3 ± 1.2

Discodermolide	0.78 ± 0.3
I-i	5.1 ± 2.2
I-ii	3.0 ± 1.0
I-iii	9.3 ± 4.0
I-iv	9.8 ± 4.9

Drug Binding Competition Assay

The assay was performed using methods described in Bollag, D.M., et al., "Epothilones, a new class of microtubule-stabilizing agents with a Taxol-like mechanism of action", *Cancer -Res.*, **1995**, 55, 2325-2333 and He, L., et al., "A common pharmacophore for Taxol and the epothilones based on the biological activity of a taxane molecule lacking a C-13 side chain", *Biochemistry*, **2000**, 39, 3972-3978. MTP (0.4 mg/ml) was incubated at 37°C with 1 mM GTP and 7.5 nM Taxol for 20 min to induce the assembly of microtubules. One hundred nanomolar [^{3}H]Taxol (specific activity: 19.3 Ci/mmol) and the indicated concentration of the competing agent were added simultaneously to the preformed microtubules. The mixtures were further incubated at 37°C for 30 min to allow binding of [^{3}H]Taxol. Microtubules were collected by ultracentrifugation (100,000 g, 1 hr, 30°C) and the radioactivity measured using a liquid scintillation counter. The inhibition of binding of [^{3}H]Taxol to microtubules was expressed as a percentage compared to the control (100%).

The assay generally probes the ability of the subject compounds to inhibit the binding of Taxol to preformed microtubules. At 1 μM, Taxol, (+)-discodermolide, and analogs I-i, I-ii, and I-iii exhibited very similar inhibition, while analog I-iv was essentially inactive in displacing [^{3}H]Taxol binding (Figure 60). Taxol and (+)-discodermolide, at 10 μM, inhibited the binding of [^{3}H]Taxol by approximately 45%. By contrast, the discodermolide analogs demonstrated between 5 and 40% inhibition. The differences between the drugs were apparent at 100 μM with

(+)-discodermolide displaying almost 95% inhibition and Taxol with 80% inhibition. Analog I-i exhibited greater than 90% inhibition. Discodermolide analogs I-ii, I-iii, and I-iv demonstrated a range of between 45 and 65% inhibition. These results are in agreement with the *in vitro* polymerization assay.

Cytotoxicity Assays

A549 cells were seeded in triplicate at a density of 1 x10^4 cells/ml in 6-well plates and allowed to attach for 24 h. After incubation with various drug concentrations for 72 h, adherent cells were trypsinized and counted (Coulter Counter model Z1; Coulter Corp., Miami, FL), and the IC_{50} was determined. SKOV3 cells were seeded at a density of 2 x 10^4 cells/ml and the above procedure followed.

Flow Cytometry

A549 cells were prepared for flow cytometry as described in Martello, L.A., et al., "Taxol and discodermolide represent a synergistic drug combination in human carcinoma cell lines", *Clin. Cancer Res.*, **2000**, 6, 1978-1987, except that drug treatment was for 24 h.

Immunofluorescence

A549 cells were prepared for immunofluorescence as described in Martello, L.A., et al., "Taxol and discodermolide represent a synergistic drug combination in human carcinoma cell lines", *Clin. Cancer Res.*, **2000**, 6, 1978-1987. In addition, cells were stained with Hoescht solution (Sigma; 1:2.5 dilution) for 15 min after the secondary antibody wash. Slides were analyzed using a Zeiss Axiophot microscope (rhodamine and DAPI filters) at x100 magnification.

(+)-Discodermolide and analogs I-i, I-ii, I-iii, and I-iv all inhibited the proliferation of A549 cells.

Taxol and analog I-i shared similar 1C$_{50}$ values, followed by (+)-discodermolide. Analog I-ii, which was as active *in vitro* as the above compounds, was approximately 2-fold less cytotoxic than (+)-discodermolide. Although analogs I-iii and I-iv both shared similar *in vitro* activity, analog I-iii had an approximately 3-fold decrease in cytotoxicity while analog I-iv had a 128-fold decrease compared to (+)-discodermolide. Similar results were obtained with SKOV3 cells, although (+)-discodermolide was approximately 8-fold less active in this cell line compared to A549 cells. Taxol and analog I-i had comparable IC$_{50}$ values, while discodermolide, analog I-ii, and analog I-iii were less cytotoxic. As seen in A549 cells, analog I-iv displayed the greatest decrease in cytotoxicity. Table 2 provides a comparison of the cytotoxicity of Taxol, discodermolide and analogs I-i, I-ii, I-iii, and I-iv in human A459 and SKOV3 cell lines.

Table 2

Compound	A549 (IC$_{50}$(μm))	SKOV3 (IC$_{50}$(μm))
Taxol	1.4 ± 0.5	3.3 ± 0.5
Discodermolide	3.8 ± 0.6	31.3 ± 6.8
I-i	1.8 ± 0.1	6.1 ± 3.7
I-ii	7.8 ± 3.3	22.0 ± 10.6
I-iii	11.4 ± 3.2	31.3 ± 16.5
I-iv	485.0 ± 6.4	353.0 ± 0.8

Under control conditions, A549 cells exhibited a normal cell cycle profile, microtubule cytoskeleton, and DNA staining (Figure 61a). Analysis by flow cytometry indicated that A549 cells are blocked in the G2/M phase of the cell cycle after exposure to a cytotoxic concentration (25 nM) of (+)-discodermolide (Figure 61b). An increase in the hypodiploid population of cells also was observed, indicating apoptosis. Microtubule bundles and condensed

nuclear DNA appeared at this concentration as shown by immunoflurescence. This effect also was seen at concentrations above 25 nM, but not at concentrations below 12 nM. Bundle formations observed with (+)-discodermolide were distinctly different from those noted with Taxol. In the presence of (+)-discodermolide, microtubule bundles were seen at the periphery of the cells, in contrast to Taxol, where the bundles were present throughout the cells (data not shown). At different cytotoxic concentrations, the discodermolide analogs caused arrest in the G2/M phase of the cell cycle and induced microtubute bundling and DNA condensation (Figure 61 c-f).

Molecular Modeling

Molecular modeling studies were performed using the Insight II software (Molecular Simulations Inc.). The α, β-tubulin structure was taken from Nogales et al. (PDB code: *1TUB*) as described in "Structure of alpha beta tubulin dimer by electron crystallography", *Nature*, **1998**, 391, 199-203. The coordinates for the Taxol X-ray structure were developed by Mastropaolo et al., "Crystal and molecular structure of Paclitaxel (Taxol)", *Proc. Natl. Acad. Sci. USA*, **1995**, 92, 6920-6924 and the Taxotere X-ray structure coordinates were acquired from Gueritte-Voegelein et al., "Structure of a synthetic taxol precursor: *N-tert*-butoxycarbonyl-10-deacetyl-*N*-debenzoyltaxol", *Acta Cryst.*, **1990**, C46, 781-784. The coordinates for (+)-discodermolide, obtained from Gunasekera et al., "Discodermolide: A new bioactive polyhydroxylated lactone from the marine sponge *Discodermia dissoluta*", *J. Org. Chem.*, **1990**, 55, 4912-4915, required sign inversion to conform to the correct absolute stereochemistry.

Both the crystal and recent solution structure of (+)-discodermolide described in Smith, A.B.I., et al., "The solution structure of (+)-discodermolide," *Org- Lett.*, *In*

Press, demonstrate that the molecule arranges the C1-C19 region into a U-shaped conformation bringing the lactone and the C19 side chain in close proximity. When overlaid with Taxol, the backbone of (+)-discodermolide mimics the northern portion of the taxane ring. The lactone and the C19 side chain of (+)-discodermolide correspond to the C13 and C2 side chains of Taxol. However, the position of the lactone and the C19 side chain with respect to the side chains of Taxol have not be determined (Figure 62 a, b). While not wishing to be bound by any particular theory, since the crystal/solution structure of the (+)-discodermolide molecule can be fitted into the Taxol binding pocket within β-tubulin in either of two orientations, two models have been proposed (Figure 62 c, d).

In model I (Figure 61 c), the C19 side chain of (+)-discodermolide, like the C2 benzoyl group of Taxol, binds in a pocket formed by His227 and Asp224 and both side chains are approximately 2-3 Å away from these amino acids. A comparison of the structures of Taxol and Taxotere, both used for the treatment of human carcinomas, shows a replacement at the C10 position (hydroxyl group) and the C3' position on the C13 side chain (tertiary butyl group) in the Taxotere structure. If Taxol is replaced by Taxotere, modeling studies have revealed a much better fit between the lactone of (+)-discodermolide and the C13 side chain of Taxotere. The C4 methyl group of the lactone is approximately 1 Å away from His227, while the tertiary butyl group is approximately 2.5 Å in distance from His227. The C11 hydroxyl group of (+)-discodermolide matches with the C10 acetyl group of Taxol and both groups are approximately 2.5 Å from Gly368. The final contact with Thr274 is made between C24 of (+)-discodermolide and the C7 hydroxyl group of Taxol, both approximately 2.8 Å from Thr274.

In model II (Figure 62 d), the lactone fits into the binding pocket formed by His227 and Asp224, in a similar manner to the C2 benzoyl group of Taxol. The C4 methyl group of the lactone is approximately 1 Å from His227 and 3

Å from Asp224. The C19 side chain of (+)-discodermolide is found near His227 (approximately 5 Å away), similar to the C3' tertiary butyl group of Taxotere. The C7 hydroxyl group of Taxol matches with the C10 methyl group of (+)-discodermolide, making contact with Thr274. The C10 methyl group is approximately 2.5 Å from the hydroxyl group of Thr274. The Gly368 contact is made between the C12 methyl group (4 Å) and C24 (1.3 Å) of (+)-discodermolide, in a similar manner to that of the C10 acetyl group of Taxol.

The four discodermolide analogs also were modeled in place of (+)-discodermolide in the β-tubulin structure. In model I, analogs I-ii and I-iii do not lose any important contacts with β-tubulin since the positions on the molecule that have been modified are not in contact with what appear to be important residues responsible for drug binding. In analog I-i, the C4 methyl group is in contact with His227 of β-tubulin while the C3 hydroxyl group that was removed did not make any significant contacts. The C14 methyl group of analog **2** and the C7 hydroxyl group of analog I-iii both are present in an open area within the drug binding pocket.

Analog I-iii may be slightly less cytotoxic due to the additive effect of removing both the C3 and C7 hydroxyl groups. A comparison of (+)-discodermolide with analog I-iv, which has the altered olefin geometry at C8, not surprisingly demonstrated a change in the conformation. Particularly, the lactone of analog I-iv is shifted, making new contacts with β-tubulin, possibly at Leu273. New interactions may explain why this analog, although less cytotoxic than other analogs, retains activity.

In model II, analogs I-i and I-ii again do not lose the necessary contacts within the drug binding pocket. Analog I-iii, however, would lose a specific contact with Arg276 that appears to be important for binding and activity, and analog I-iv would lose all contacts, including those with His227 and Asp224. Moreover, the lactone of analog I-iv would now point out of the binding pocket towards the lumen of the microtubule structure. Since

analog I-iii does not demonstrate a significant decrease in cytotoxicity and analog I-iv retains activity in the high nM range, model II is not supported. Therefore, we favor model I as the orientation of (+)-discodermolide within the β-tubulin structure.

Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting.

EXAMPLES

EXAMPLE 1

Alcohol (-)-8.

p-Methoxybenzyl alcohol (200 g, 1.45 mol) was added to a suspension of NaH (60% in mineral oil; 5.82 g, 0.146 mol) in anhydrous ether (450 mL) over 1 h at room temperature. The mixture was stirred for 1 h and cooled to 0 °C. Trichloroacetonitrile (158 mL, 1.58 mol) was then introduced over 80 min. After 1.5 h the solution was concentrated with the water bath temperature maintained below 40 °C. The residue was treated with a mixture of pentane (1.5 L) and MeOH (5.6 mL), stirred at room temperature for 30 min, and filtered through a short Celite column. Concentration gave the trichloroimidate (394.3 g) as a red oil which was used without further purification.

A solution of (*R*)-(-)-Roche ester (124.7 g, 1.06 mol) in CH_2Cl_2/cyclohexane (1:2, 1.5 L) was cooled to 0 °C and treated with trichloroimidate (364.3 g) and PPTS (13.3 g, 52.9 mmol). After 3 h, the mixture was warmed to room temperature, stirred for 40 h, and concentrated. Filtration through a short silica column (20% ethyl acetate/hexane)

afforded the ester (303.5 g) as a slight yellow oil.

The ester (303.5 g) was divided into three portions for the next reaction. In each preparation, solution of crude ester (112.8 g) in anhydrous THF (1.0 L) was cooled to 0 °C and $LiAlH_4$ (1.0 M in THF, 560 mL, 0.560 mol) was added over 1 h. The mixture was warmed gradually to room temperature and stirred for 24 h. After dilution with ether (1.0 L) the mixture was cooled to 0 °C and quenched carefully with saturated aqueous Rochelle's salt (20 mL). The resultant mixture was then transferred to a 4-L flask, diluted with ether (1.0 L), and treated with additional Rochelle's solution (ca. 300 mL) with shaking until a solid precipitated. The solution was filtered, concentrated, and the residue (including the aqueous layer) was diluted with ether (700 mL), dried over Na_2SO_4, filtered and concentrated. The crude products of the three reactions were combined and distilled under vacuum, furnishing (-)-**8** (142.7 g, 74% yield for two steps) as a colorless oil: $[\alpha]^{23}_D$ -16.9° © 1.28, $CHCl_3$); IR ($CHCl_3$) 3510 (m), 3015 (s), 2965 (s), 2940 (s), 2920 (s), 2870 (s), 2840 (m), 1618 (s), 1590 (m), 1517 (s), 1470 (s), 1445 (m), 1423 (m), 1365 (m), 1305 (s), 1250 (s), 1178 (s), 1092 (s), 1037 (s), 826 (m), 814 (m), 718 (w), 710 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.23 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 4.43 (ABq, J_{AB} = 11.7 Hz, $\Delta\delta_{AB}$ = 13.2 Hz, 2 H), 3.78 (s, 3 H), 3.61-3.54 (m, 2 H), 3.53 (ddd, J = 9.1, 4.7, 0.8 Hz, 1 H), 3.38 (dd, J = 9.1, 7.9 Hz, 1 H), 2.60 (br s, 1 H), 2.08-1.98 (m, 1 H), 0.90 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.2, 130.2, 129.2, 113.8, 75.0, 73.0, 67.7, 55.2, 35.6, 13.4; high resolution mass spectrum (CI, NH_3) *m/z* 210.1252 [M^+; calcd for $C_{12}H_{18}O_3$: 210.1256].

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.60.

EXAMPLE 2

Aldol (+)-10.

A solution of DMSO (40.0 mL, 564 mmol) in CH_2Cl_2 (1.0 L) was cooled to -78 °C and oxalyl chloride (23.0 mL, 263 mmol) was added over 1 h. After an additional 15 min, a cooled (-78 °C) solution of alcohol (-)-8 (38.0 g, 181 mmol) in CH_2Cl_2 (50 mL) was introduced via a cannula over 15 min (20 mL rinse) and the resultant milky mixture was stirred 0.5 h further at -78 °C. *I*-Pr_2NEt (150 mL, 861 mmol) was then added over 15 min. The mixture was stirred for 30 min, slowly warmed to room temperature (70 min), and quenched with aqueous $NaHSO_4$ (1.0 M, 1.0 L). The organic phase was concentrated, diluted with ether (500 mL), washed with water (6 x 500 mL), dried over $MgSO_4$, filtered and concentrated to give the corresponding aldehyde (38.0 g) as a colorless oil.

A solution of oxazolidinone (+)-**9** (44.3 g, 190 mmol) in CH_2Cl_2 (500 mL) was cooled to 0 °C. *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 199.0 mL, 199 mmol) was introduced over 0.5 h, followed by addition of NEt_3 (30.2 mL, 217 mmol) over 10 min. The mixture was stirred at 0 °C for 0.5 h and cooled to -78 °C. A precooled (-78 °C) solution of the above aldehyde in CH_2Cl_2 (100mL) was then added via a cannula over 30 min (2 x 20mL rinse). After 2 h at -78 °C and 2 h at 0 °C, the reaction was quenched with pH 7 phosphate buffer (200 mL). The mixture was slowly treated with a solution of 30% H_2O_2 in MeOH (1:2, 600 mL) at 0 °C, stirred overnight at room temperature, and concentrated. The residue was extracted with ethyl acetate (3 x 250 mL) and the combined extracts were washed with saturated aqueous $NaHCO_3$ and water (500 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (30% ethyl acetate/hexane) provided (+)-**10** (70.9 g, 89% yield from **8**) as a colorless oil: $[\alpha]^{23}_D$ +278° (c 0.49, $CHCl_3$); IR ($CHCl_3$) 3470 (w, br), 3020 (m), 2980 (m), 2940 (m), 2920 (m), 2880 (m), 1790 (s), 1705 (m), 1620 (m), 1590 (w), 1520 (m), 1485 (w), 1460 (m), 1390 (m), 1360 (m), 1305 (w), 1230 (br, s), 1110 (m), 1080 (m), 1035 (m), 985

(m), 970 (m), 820 (w), 695 (w) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.33-7.30 (m, 2 H), 7.27-7.19 (m, 5 H), 6.85 (d, J = 8.7 Hz, 2 H), 4.67-4.63 (m, 1 H), 4.42 (apparent s, 2 H), 4.14 (apparent d, J = 5.0 Hz, 2 H), 3.93 (qd, J = 6.9, 3.4 Hz, 1 H), 3.85 (ddd, J = 8.2, 3.1, 3.1 Hz, 1 H), 3.78 (s, 3 H), 3.69 (d, J = 2.8 Hz, 1 H), 3.54 (apparent t, J = 9.3 Hz, 1 H), 3.54 (dd, J = 21.1, 9.2 Hz, 1 H), 3.28 (dd, J = 13.4, 3.2 Hz, 1 H), 2.76 (dd, J = 13.4, 9.6 Hz, 1 H), 1.98-1.93 (m, 1 H), 1.25 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) δ 176.1, 159.2, 153.0, 135.3, 129.9, 129.3, 129.2, 128.8, 127.2, 113.7, 75.3, 74.5, 73.1, 66.0, 55.5, 55.2, 40.6, 37.7, 35.9, 13.5, 9.7; high resolution mass spectrum (CI, NH_3) m/z 442.2243 [$(M+H)^+$; calcd for $C_{25}H_{32}NO_6$: 442.2229].

Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08. Found: C, 67.81; H, 7.26.

EXAMPLE 3

Common Precursor (+)-5.

A suspension of N,O-Dimethylhydroxylamine hydrochloride (46.9 g, 481 mmol) in THF (250 mL) was cooled to 0 °C and $AlMe_3$ (2.0 M in hexane, 240 mL, 480 mmol) was added over 30 min. The resultant solution was warmed to room temperature, stirred for 0.5 h and then cooled to -30 °C. A solution of oxazolidinone (+)-**10** (70.9 g, 161 mmol) in THF (150 mL) was introduced over 20 min via cannula (20 mL rinse). After 3 h, the solution was poured slowly into a mixture of aqueous HCl (1.0 N, 1.2 L) and CH_2Cl_2 (1.0 L) at 0 °C and the mixture was shaken vigorously for 1 h. The aqueous phase was extracted with CH_2Cl_2 (2 x 500 mL) and the combined organic extracts were washed with water (3 x 1.0 L), dried over $MgSO_4$, filtered and concentrated. The crude material was taken up in ethyl acetate/hexane (1:3, 150 mL) with vigorous stirring to precipitate most of the chiral auxiliary. Filtration, concentration and flash

chromatography (20% acetone/hexane) afforded (+)-**5** (46.2 g, 88% yield) as a colorless oil: $[\alpha]^{23}_D$ +144° © 0.41, $CHCl_3$); IR ($CHCl_3$) 3470 (m, br), 3010 (s), 2975 (s), 2945 (s), 2915 (s), 2870 (s), 2845 (m), 1680 (s), 1590 (w), 1515 (s), 1465 (s), 1425 (m), 1390 (m), 1365 (m), 1310 (m), 1250 (s), 1180 (s), 1150 (m), 1090 (s), 1040 (s), 1000 (s), 825 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.44 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 17.1 Hz, 2 H), 3.95 (d, J = 2.8 Hz, 1 H), 3.79 (s, 3 H), 3.70 (ddd, J = 8.2, 3.2, 3.2 Hz, 1 H), 3.66 (s, 3 H), 3.62 (dd, J = 9.0, 4.0 Hz, 1 H), 3.53 (dd, J = 9.1, 5.9 Hz, 1 H), 3.17 (s, 3 H), 3.04 (m, 1 H), 1.91-1.84 (m, 1 H), 1.17 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 178.0, 159.0, 130.6, 129.1, 113.7, 113.6, 73.8, 72.8, 72.6, 61.3, 55.1, 36.5, 36.0, 14.2, 10.4; high resolution mass spectrum (CI, NH_3) *m/z* 326.1962 [$(M+H)^+$; calcd for $C_{17}H_{28}NO_5$: 326.1967].

Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.74; H, 8.36. Found: C, 62.74; H, 8.24.

EXAMPLE 4

Weinreb Amide (-)-11.

A mixture of common precursor (+)-**5** (337.3 mg, 1.04 mmol), 4 Å molecular sieves (344 mg), and CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with DDQ (310.3 mg, 1.37 mmol). After 1.5 h, the mixture was filtered through a short Celite column (50% ethyl acetate/hexane). The filtrate was washed with saturated aqueous $NaHCO_3$ and water (100 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (30% ethyl acetate/hexane) provided (-)-**11** (255.6 mg, 76% yield) as a colorless oil: $[\alpha]^{23}_D$ -339° © 0.520, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 2970 (s), 2940 (m), 2880 (m), 2840 (m), 1663 (s), 1620 (s), 1592 (w), 1520 (s), 1466 (s), 1447 (m), 1425 (m), 1393 (s), 1375 (s), 1307 (m), 1253 (s), 1178 (s),

1120 (s), 1083 (s), 1035 (s), 1015 (m), 1000 (s), 930 (w), 830 (m), 700 (w), 660 (w), 620 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.41 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 5.46 (s, 1 H), 4.04 (dd, J = 11.3, 4.7 Hz, 1 H), 3.82 (dd, J = 9.8, 6.5 Hz, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.51 (apparent t, J = 11.2 Hz, 1 H), 3.19 (s, 3 H), 3.21-3.14 (m, 1 H), 1.98-1.92 (m, 1 H), 1.27 (d, J = 7.0 Hz, 3 H), 0.75 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 175.8, 159.8, 131.2, 127.2, 113.5, 100.7, 82.8, 72.8, 61.3, 55.3, 39.0, 33.8, 32.6, 13.1, 12.4; high resolution mass spectrum (CI, NH_3) *m/z* 323.1736 [M^+; calcd for $C_{17}H_{25}NO_5$: 323.1732].

Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79. Found: C, 63.18; H, 7.74.

EXAMPLE 5

Aldehyde (-)-12.

A solution of amide (-)-**11** (2.07 g, 6.40 mmol) in THF (70 mL) was cooled to -78 °C and $LiAlH_4$ (1.0 M in THF, 3.40 mL, 3.40 mmol) was added over 15 min. After 10 min at -78 °C and 10 min at 0 °C, the mixture was quenched with MeOH (1.0 mL), and partitioned between ethyl acetate and saturated aqueous Rochelle's salt (100 mL each). The organic phase was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (15% ethyl acetate/hexane) gave (-)-**12** (1.38 g, 80% yield) as a colorless oil: $[\alpha]^{23}_D$ -7.8° © 0.46, $CHCl_3$); IR ($CHCl_3$) 3015 (m), 2970 (m), 2940 (m), 2840 (m), 1735 (s), 1725 (s), 1615 (m), 1590 (w), 1520 (s), 1460 (s), 1390 (m), 1370 (m), 1305 (m), 1250 (s), 1170 (s), 1115 (s), 1085 (s), 1035 (s), 990 (m), 960 (m), 830 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 9.74 (apparent s, 1 H), 7.32 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 5.46 (s, 1 H), 4.13 (dd, J = 11.5, 4.8 Hz, 1 H), 4.05 (dd, J = 10.4, 2.6 Hz, 1 H), 3.77 (s, 3 H), 3.56

(apparent t, J = 11.1 Hz, 1 H), 2.56 (qd, J = 7.1, 2.6 Hz, 1 H), 2.15-2.03 (m, 1 H), 1.23 (d, J = 7.1 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) δ 204.0, 159.9, 130.7, 127.2, 113.5, 100.9, 81.6, 72.8, 55.2, 47.4, 30.3, 11.9, 7.1; high resolution mass spectrum (CI, NH_3) *m/z* 265.1432 [$(M+H)^+$; calcd for $C_{15}H_{21}O_4$: 265.1439].

EXAMPLE 6

Aldol (+)-13.

A solution of oxazolidinone (+)-**9** (21.6 g, 92.7 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C and n-Bu_2BOTf (1.0 M in CH_2Cl_2, 86.1 mL, 86.1 mmol) was added over 0.5 h, followed by addition of NEt_3 (15.7 mL, 112.5 mmol) over 10 min. The mixture was stirred at 0 °C for 1 h and cooled to -78 °C. A solution of aldehyde (-)-**12** (17.5 g, 66.2 mmol) in CH_2Cl_2 (50 mL) was added over 10 min. After additional 20 min at -78 °C and 1 h at 0 °C, the reaction was quenched with pH 7 phosphate buffer (100 mL) and MeOH (300 mL), then slowly treated with a solution of 30% H_2O_2 in MeOH (1:1, 100 mL) at 0 °C. After 1 h, saturated aqueous $Na_2S_2O_3$ (100 mL) was added. The mixture was concentrated and the residue was extracted with ethyl acetate (3 x 250 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$ (10%), brine (200 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) provided (+)-**13** (26.3 g, 80% yield) as white crystals: mp 98-100 °C; $[\alpha]^{23}_D$ +13.5° © 1.19, $CHCl_3$); IR ($CHCl_3$) 3690 (w), 3520 (w, br), 3020 (m), 2980 (m), 2940 (m), 2880 (w), 2850 (m), 1790 (s), 1695 (m), 1620 (m), 1595 (w), 1525 (m), 1505 (w), 1490 (w), 1465 (m), 1390 (s), 1365 (m), 1310 (m), 1260-1210 (m, br), 1175 (m), 1120 (s), 1085 (m), 1040 (m), 1020 (m), 985 (m), 970 (m), 930 (w), 830 (m), 700 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.35 (d, J = 8.7 Hz, 2 H), 7.31 (d, J = 7.6 Hz, 2 H), 7.27 (d, J = 7.2 Hz, 1 H), 7.19 (d, J = 7.7 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 5.45 (s, 1

H), 4.67-4.62 (m, 1 H), 4.14 (apparent d, J = 5.3 Hz, 2 H), 4.08 (dd, J = 11.4, 4.8 Hz, 1 H), 4.07 (apparent t, J = 4.1 Hz, 1 H), 4.04-3.99 (m, 1 H), 3.76 (s, 3 H), 3.61 (dd, J = 9.9, 2.2 Hz, 1 H), 3.51 (apparent t, J = 11.1 Hz, 1 H), 3.33 (d, J = 1.3 Hz, 1 H), 3.21 (dd, J = 13.4, 3.4 Hz, 1 H), 2.76 (dd, J = 13.4, 9.4 Hz, 1 H), 2.12-2.06 (m, 1 H), 1.92-1.86 (m, 1 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.74 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) δ 177.1, 160.0, 152.7, 135.0, 131.0, 129.4, 128.9, 127.40, 127.39, 113.6, 101.2, 85.8, 74.5, 73.0, 66.0, 55.2, 54.9, 39.8, 37.7, 35.7, 30.4, 12.8, 11.7, 7.8; high resolution mass spectrum (CI, NH_3) m/z 497.2410 [M^+; calcd for $C_{28}H_{35}NO_7$: 497.2413].

Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.58; H, 7.09. Found: C, 67.42; H, 7.02.

EXAMPLE 7

Acetal (+)-14.

A solution of alcohol (+)-**13** (26.3 g, 52.9 mmol) and 2,6-lutidine (11.1 mL, 95.3 mmol) in CH_2Cl_2 (150 mL) was cooled to -20°C and TBSOTf (20.5 mL, 79.3 mmol) was added over 30 min. After additional 2 h at 0 °C, the mixture was diluted with ether (300 mL), washed with aqueous $NaHSO_4$ (1.0 M, 200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (gradient elution, 5% -> 10% ethyl acetate/hexane) afforded (+)-**14** (32.4 g, 100% yield) as a colorless oil: $[\alpha]^{23}_D$ +20.3° © 1.32, $CHCl_3$); IR ($CHCl_3$) 3025 (m), 2970 (m), 2940 (m), 2864 (m), 1788 (s), 1705 (m), 1620 (m), 1597 (w),1524 (m), 1503 (w), 1470 (m), 1447 (w), 1430 (w), 1395 (s), 1358 (m), 1307 (m), 1255 (s), 1135 (m), 1120 (s), 1075 (m), 1030 (m), 985 (m), 976 (m), 930 (m), 865 (m), 838 (s), 813 (m), 790 (m), 700 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.38 (d, J = 8.7 Hz, 2 H), 7.30-7.12 (m, 5 H), 6.82 (d, J = 8.7 Hz, 2 H), 5.44 (s, 1 H), 4.30

(dddd, J = 13.4, 7.3, 5.1, 5.1 Hz, 1 H), 4.11 (dd, J = 7.1, 4.0 Hz, 1 H), 4.02 (dd, J = 11.2, 4.7 Hz, 1 H), 3.97 (dq, J = 7.0, 7.0 Hz, 1 H), 3.80 (dd, J = 8.9, 2.3 Hz, 1 H), 3.740 (apparent t, J = 4.9 Hz, 1 H), 3.738 (s, 3 H), 3.48 (apparent t, J = 11.1 Hz, 1 H), 3.27 (apparent t, J = 8.2 Hz, 1 H), 3.15 (dd, J = 13.4, 3.2 Hz, 1 H), 2.59 (dd, J = 13.4, 9.8 Hz, 1 H), 2.05 (apparent qd, J = 7.4, 4.2 Hz, 1 H), 2.02-1.94 (m, 1 H), 1.19 (d, J = 6.9 Hz, 1 H), 1.04 (d, J = 7.5 Hz, 3 H), 0.92 (s, 9 H), 0.73 (d, J = 6.7 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 175.6, 159.9, 152.4, 135.5, 132.0, 129.4, 128.8, 127.8, 127.2, 113.4, 100.7, 80.7, 74.6, 73.1, 65.3, 55.3, 55.2, 41.4, 40.9, 37.4, 30.6, 26.0, 18.1, 15.0, 12.7, 11.5, -4.0, -4.6; high resolution mass spectrum (CI, NH_3) *m/z* 612.3340 [$(M+H)^+$; calcd for $C_{34}H_{50}NO_7Si$: 612.3356].

Anal. Calcd for $C_{34}H_{49}NO_7Si$: C, 66.74; H, 8.07. Found: C, 66.69; H, 7.98.

EXAMPLE 8

Alcohol (-)-15.

A solution of acetal (+)-**14** (32.0 g, 52.3 mmol) in THF (600 mL) was cooled to -30 °C and EtOH (6.14 mL, 105 mmol) was added, followed by addition of $LiBH_4$ (2.0 M in THF, 52.3 mL, 105 mmol) over 15 min. After additional 1 h at 0 °C and 12 h at room temperature, the mixture was diluted with ether (1.0 L), quenched carefully with aqueous NaOH (1.0 N, 200 mL) and stirred for 2 h at room temperature. The layers were separated and the organic phase was washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (20% ethyl acetate/hexane) provided (-)-**15** (18.7 g, 81% yield) as a colorless oil: $[\alpha]^{23}_D$ -36.1° © 1.15, $CHCl_3$); IR ($CHCl_3$) 3630 (w), 3480 (w, br), 3010 (m), 2960 (s), 2940 (s), 2885 (m), 2860 (s), 1620 (m), 1594 (w), 1523 (s), 1468 (s), 1445 (w),

1430 (w), 1395 (m), 1365 (m), 1307 (m), 1255 (s), 1175 (m), 1165 (m),1150 (m), 1120 (s), 1080 (s), 1030 (s), 990 (m), 968 (m), 910 (s), 860 (m), 833 (s), 700 (m), 645 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.36 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 5.38 (s, 1 H), 4.08 (dd, J = 11.2, 4.7 Hz, 1 H), 3.84 (dd, J = 6.7, 1.9 Hz, 1 H), 3.77 (s, 3 H), 3.53 (dd, J = 9.9, 1.8 Hz, 1 H), 3.55-3.52 (m, 1 H), 3.47 (apparent t, J = 11.1 Hz, 1 H), 3.44 (dd, J = 10.3, 6.2 Hz, 1 H), 2.08-1.97 (m, 2 H), 1.94 (dqd, J = 7.1, 7.1, 1.7 Hz, 1 H), 1.76 (br s, 1 H), 1.02 (d, J = 7.1, 3 H), 0.88 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.73 (d, J = 6.7 Hz, 3 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 131.4, 127.3, 113.5, 101.0, 82.9, 74.3, 73.3, 66.3, 55.2, 38.7, 37.8, 30.7, 26.1, 18.3, 12.2, 11.1, 10.7, -4.0, -4.2; high resolution mass spectrum (CI, NH_3) *m/z* 439.2889 [$(M+H)^+$; calcd for $C_{24}H_{43}O_5Si$: 439.2879].

Anal. Calcd for $C_{24}H_{42}O_5Si$: C, 65.71; H, 9.65. Found: C, 65.51; H 9.54.

EXAMPLE 9

Tosylate (-)-16.

A solution of alcohol (-)-**15** (5.00 g, 11.4 mmol) in anhydrous pyridine (30 mL) was cooled to 0 °C and treated with TsCl (3.91 g, 20.5 mmol). After 30 min at 0 °C and 5 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was diluted with ether (200 mL), washed with aqueous $NaHSO_4$ (1.0 M), aqueous $NaHCO_3$ (10%), brine (200 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) provided (-)-**15** (6.76 g, 100% yield) as white solid: mp 71-72 °C; $[\alpha]^{23}_{D}$ -23.2° © 1.42, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 3000 (m), 2960 (s), 2935 (s), 2880 (m), 2855 (s), 1617 (m), 1600 (m), 1590 (m), 1518 (m), 1495 (w), 1462 (s), 1390 (m), 1360 (s), 1302 (m), 1250 (s), 1190 (s),

1178 (s), 1120 (s), 1098 (s), 1085 (s), 1070 (s, 1032 (s), 963 (s), 900 (m), 830 (s), 810 (s), 653 (m); ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.70 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.7 Hz, 2 H), 7.25 (d, J = 8.8 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 5.36 (s, 3 H), 4.07 (dd, J = 11.2, 4.7 Hz, 1 H), 3.85 (dd, J = 7.3, 2.7 Hz, 1 H), 3.79 (s, 3 H), 3.71 (dd, J = 7.1, 1.7 Hz, 1 H), 3.48 (dd, J = 9.9, 1.4 Hz, 1 H), 3.45 (apparent t, J = 11.1 Hz, 1 H), 2.40 (s, 3 H), 2.15 (dqd, J = 13.9, 7.0, 1.7 Hz, 1 H), 2.05-1.96 (m, 1 H), 1.83 (dqd, J = 7.1, 7.1, 1.6 Hz, 1 H), 0.94 (d, J = 7.1 Hz, 3 H), 0.82 (s, 9 H), 0.81 (d, J = 7.7 Hz, 3 H), 0.69 (d, J = 6.7 Hz, 3 H), -0.04 (s, 3 H), -0.11 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 144.6, 133.2, 131.3, 129.7, 127.9, 127.3, 113.5, 100.9, 82.0, 73.7, 73.2, 73.0, 55.2, 38.4, 35.5, 30.6, 26.0, 21.6, 18.3, 12.2, 10.6, 10.3, -3.9, -4.3; high resolution mass spectrum (FAB, NBA) *m/z* 593.2955 [$(M+H)^+$; calcd for $C_{31}H_{49}O_7SSi$: 593.2968].

EXAMPLE 10

Fragment (-)-A. From Tosylate (-)-**16**: A solution of Tosylate (-)-**16** (6.76 g, 11.4 mmol) in anhydrous DMF (50 mL) was treated with NaI (17.1 g, 114.0 mmol), heated at 60 °C for 1.5 h, and cooled to room temperature. The mixture was diluted with ether (200 mL), washed with water (200 mL), saturated aqueous $Na_2S_2O_3$ (100 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (3% ethyl acetate/hexane) provided (-)-**A** (5.87 g, 94 % yield) as a colorless oil.

From Alcohol (-)-**15**: A solution of alcohol (-)-**15** (4.70 g, 10.7 mmol), PPh_3 (4.21 g, 16.1 mmol) and imidazole (1.09 g, 16.1 mmol) in benzene/ether (1:2, 75 mL) was treated with I_2 (4.08 g, 16.1 mmol) under vigorous stirring. The mixture was stirred 1 h then diluted with ether (200 mL), washed with saturated $Na_2S_2O_3$, brine (100 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography

(2% ethyl acetate/hexane) furnished (-)-**A** (5.56 g, 95% yield) as a colorless oil: $[\alpha]^{23}_D$ -39.3° © 2.01, $CHCl_3$); IR ($CHCl_3$) 3015 (m), 2960 (s), 2940 (s), 2860 (m), 1620 (w), 1520 (m), 1465 (m), 1430 (w), 1390 (m), 1305 (w), 1255 (s), 1230 (m), 1215 (m), 1205 (m), 1170 (m), 1120 (m), 1070 (m), 1035 (m), 990 (w), 970 (w), 930 (w), 830 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.39 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 5.40 (s, 1 H), 4.09 (dd, J = 11.2, 4.7 Hz, 1 H), 3.85 (dd, J = 7.1, 1.9 Hz, 1 H), 3.79 (s, 3 H), 3.48 (dd, J = 8.2, 1.5 Hz, 1 H), 3.47 (apparent t, J = 11.1 Hz, 1 H), 3.18-3.12 (m, 2 H), 2.11-2.00 (m, 2 H), 1.84 (ddq, J = 7.1, 7.1, 1.6 Hz, 1 H), 1.02 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.72 (d, J = 6.7 Hz, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 131.4, 127.4, 113.4, 100.9, 82.4, 75.5, 73.2, 55.3, 39.6, 38.7, 30.7, 26.2, 18.4, 14.7, 14.5, 12.2, 10.7, -3.7, -3.8; high resolution mass spectrum (CI, NH_3) *m/z* 548.1833 [$(M)^+$; calcd for $C_{24}H_{41}IO_4Si$: 548.1819].

Anal. Calcd for $C_{24}H_{41}O_4ISi$: C, 52.55; H, 7.53. Found: C, 52.77; H, 7.68.

EXAMPLE 11

Amide (+)-17.

A solution of common precursor (+)-**5** (12.1 g, 37.2 mmol) and 2,6-lutidine (7.80 mL, 70.0 mmol) in CH_2Cl_2 (90 mL) was cooled to 0°C and *tert*-Butyldimethylsilyl trifluoromethanesulfonate (12.8 mL, 55.8 mmol) was added over 10 min. After 1.5 h, the mixture was diluted with Et_2O (100 mL), washed with aqueous $NaHSO_4$ (1.0 M), brine (200 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexanes) provided (+)-**17** (16.4 g, 100% yield) as a colorless oil: $[\alpha]^{23}_D$ +9.49° © 1.47, $CHCl_3$); IR ($CHCl_3$) 3018 (s), 2970 (s), 2945 (s), 2900 (m), 2870 (s), 1658 (s),1620 (m), 1592 (w), 1520 (s), 1470

(s), 1448 (m), 1425 (m), 1393 (m), 1367 (m), 1308 (m), 1255 (s), 1213 (s), 1185 (m), 1178 (m), 1115 (s), 1084 (s), 1042 (s), 1000 (s), 940 (w), 928 (w), 871 (s), 839 (s), 770 (s), 726 (s), 664 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.21 (d, J = 8.7 Hz, 2 H), 6.83 (d, J = 8.7, 2 H), 4.36 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 17.3 Hz, 2 H), 3.92 (dd, J = 8.2, 3.0 Hz, 1 H), 3.77 (s, 3 H), 3.55 (s, 3 H), 3.54 (dd, J = 9.2, 2.5 Hz, 1 H), 3.13 (dd, J = 9.2, 7.8 Hz, 1 H), 3.09 (s, 3 H), 3.15-3.09 (m, 1 H), 1.92-1.87 (m, 1 H), 1.09 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.04 (apparent s, 6 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 176.8, 159.1, 130.9, 129.2, 113.7, 76.0, 72.7, 71.9, 61.1, 55.2, 39.3, 38.9, 26.1, 18.4, 15.3, 15.0, -3.87, -3.93; high resolution mass spectrum (CI, NH_3) *m/z* 440.2823 [$(M+H)^+$; calcd for $C_{23}H_{42}NO_5Si$: 440.2832].

Anal. Calcd for $C_{23}H_{41}NO_5Si$: C, 62.83; H, 9.40. Found: C, 63.05; H, 9.32.

EXAMPLE 12

Aldehyde (+)-18.

A solution of amide (+)-**17** (9.19 g, 20.9 mmol) in THF (350 mL) was cooled to -78 °C and DIBAL (1.0 M in hexane, 44.0 mL, 44.0 mmol) was added over 30 min. After 0.5 h at -78 °C, the reaction was quenched with MeOH (10 mL). The mixture was diluted with ether (500 mL), washed with saturated aqueous Rochelle's salt, brine (300 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) gave (+)-**18** (7.05 g, 89% yield) as a colorless oil: $[\alpha]^{23}_{D}$ +23.2° © 1.49, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2930 (s), 2860 (s), 1730 (s), 1610 (m), 1583 (w), 1510 (m), 1460 (m), 1373 (m), 1360 (w), 1300 (m), 1245 (s), 1170 (m), 1085 (m), 1033 (s), 933 (w), 835 (s) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 9.67 (d, J = 0.9 Hz, 1 H), 7.22 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H),

4.37 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 23.6 Hz, 2 H), 4.18 (dd, J = 6.1, 3.7 Hz, 1 H), 3.78 (s, 3 H), 3.41 (dd, J = 9.2, 5.7 Hz, 1 H), 3.31 (dd, J = 9.2, 6.0 Hz, 1 H), 2.47 (qdd, J = 7.1, 3.7, 0.9 Hz, 1 H), 2.03-1.95 (m, 1 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.84 (s, 9 H), 0.04 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 204.8, 159.2, 130.5, 129.2, 113.8, 72.7, 72.4, 71.7, 55.3, 50.0, 38.3, 25.9, 18.2, 14.3, 8.4, -4.1, -4.4; high resolution mass spectrum (FAB, NBA) m/z 403.2304 [$(M+Na)^+$; calcd for $C_{21}H_{36}O_4SiNa$: 403.2280].

EXAMPLE 13

Bromo Ester 19.

A solution of aldehyde (+)-**18** (822.1 mg, 2.16 mmol) in benzene (20 mL) was treated with Ph_3P=$CBrCO_2Et$ (2.28 g, 5.34 mmol), heated at reflux for 40 h and cooled to room temperature. The mixture was filtered through a short silica column (20% ethyl acetate/hexane) and concentrated. Flash chromatography (3% ethyl acetate/hexane) afforded Z-Bromo ester (-)-**19** (861.4 mg, 75% yield) and E-Bromo Ester (+)-**19** (101.0 mg, 8.8% yield).

Z-Bromo Ester (-)-**19**: Colorless oil; $[\alpha]^{23}_D$ -6.38° © 1.85, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2940 (s), 2860 (s), 1725 (s), 1618 (m), 1590 (w), 1515 (s), 1468 (m), 1390 (m), 1370 (m), 1303 (m), 1250 (s, br), 1176 (m), 1090 (s), 1037 (s), 1008 (m), 950 (m), 940 (m), 840 (s) cm^{-1}; ^1H NMR (500 MHZ, C_6D_6) d 7.45 (d, J = 9.7 Hz, 1 H), 7.26 (d, J = 8.6 Hz, 2 H), 6.80 (d, J = 8.7 Hz, 2 H), 4.37 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 19.3 Hz, 2 H), 3.99, (dq, J = 10.8, 7.1 Hz, 1 H), 3.94 (dq, J = 10.8, 7.1 Hz, 1 H), 3.82 (apparent t, J = 5.4 Hz, 1 H), 3.41 (dd, J = 9.1, 6.3 Hz, 1 H), 3.31 (s, 3 H), 3.30 (dd, J = 9.2, 6.5 Hz, 1 H), 3.13-3.06 (m, 1 H), 2.05 (apparent septet, J = 6.9 Hz, 1 H), 1.013 (d, J = 7.0 Hz, 3 H), 1.006

(d, J = 6.8 Hz, 3 H), 0.97 (s, 9 H), 0.92 (apparent t, J = 7.1 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 162.5, 159.1, 149.6, 130.8, 129.0, 114.9, 113.7, 75.5, 72.6, 72.2, 62.4, 55.3, 40.2, 38.9, 26.0, 18.3, 14.2, 14.1, 13.7, -4.0, -4.2; high resolution mass spectrum (CI, NH_3) m/z 546.2270 [$(M+NH_4)^+$; calcd for $C_{25}H_{45}NO_5BrSi$: 546.2251].

Anal. Calcd for $C_{25}H_{41}O_5BrSi$: C, 56.70; H, 7.80. Found: C, 56.96; H, 7.86.

E-Bromo Ester (+)-**19**. Colorless oil; $[\alpha]^{23}_D$ +3.2° © 1.65, $CHCl_3$); IR ($CHCl_3$) 2965 (s), 2940 (s), 2905 (m), 2890 (m), 2865 (s), 1720 (s), 1617 (m), 1590 (w), 1518 (s), 1468 (s), 1375 (s), 1350 (m), 1305 (m), 1250 (s, br), 1177 (m), 1090 (s), 1035 (s), 1007 (m), 950 (m), 840 (s), 675 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.23 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.56 (d, J = 10.6 Hz, 1 H), 4.39 (apparent s, 2 H), 4.24 (dq, J = 10.8, 7.1 Hz, 1 H), 4.22 (dq, J = 10.8, 7.1 Hz, 1 H), 3.79 (s, 3 H), 3.61 (dd, J = 5.5, 5.0 Hz, 1 H), 3.43 (dd, J = 9.2, 5.5 Hz, 1 H), 3.39-3.32 (m, 1 H), 3.24 (dd, J = 9.1, 7.2 Hz, 1 H), 1.98-1.90 (m, 1 H), 1.30 (apparent t, J = 7.1 Hz, 1 H), 1.00 (d, J = 6.7 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 162.8, 159.1, 151.9, 130.8, 129.1, 113.7, 110.2, 76.3, 72.6, 72.2, 62.1, 55.2, 38.8, 26.1, 18.3, 14.7, 14.1, 13.9, -4.06, -4.10; high resolution mass spectrum (CI, NH_3) m/z 529.1982 [$(M+H)^+$; calcd for $C_{25}H_{42}BrO_5Si$: 529.1985].

Anal. Calcd for $C_{25}H_{41}O_5BrSi$: C, 56.70; H, 7.80. Found: C, 56.83; H, 7.99.

EXAMPLE 14

Allylic Alcohol (-)-20.

A solution of ester (-)-**19** (858.4 mg, 1.62 mmol) in CH_2Cl_2 (16 mL) was cooled to -78°C and DIBAL (1.0 M in hexane, 3.60 mL, 3.60 mmol) was added over 10 min. After 5

min at -78 °C and 10 min at room temperature, the reaction was quenched with MeOH (200 mL), followed by addition of saturated aqueous Rochelle's salt dropwise with stirring until a solid precipitated. The solution was separated by decanting (3 x 30 mL rinse, ethyl acetate) and the combined organic solutions were dried over $MgSO_4$, and concentrated. Flash chromatography (10% ethyl acetate/hexane) provided (-)-**20** (674.5 mg, 85% yield) as a colorless oil: $[\alpha]^{23}_D$ -15.5° © 2.51, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3420 (w, br), 3010 (m), 2960 (s), 2940 (s), 2890 (m), 2860 (s), 1618 (m), 1590 (w), 1520 (s), 1470 (m), 1380 (m), 1315 (m), 1307 (m), 1255 (s), 1178 (m), 1085 (s), 1039 (s), 1010 (m), 972 (m), 940 (m), 840 (s), 675 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.24 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.88 (br d, J = 9.3 Hz, 1 H), 4.39 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 18.3 Hz, 2 H), 4.16 (apparent d, J = 5.6 Hz, 2 H), 3.79 (s, 3 H), 3.59 (apparent t, J = 5.3 Hz, 1 H), 3.48 (dd, J = 9.2, 5.3 Hz, 1 H), 3.23 (dd, J = 9.2, 7.7 Hz, 1 H), 2.82-2.76 (m, 1 H), 2.00-1.92 (m, 1 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.024 (s, 3 H), 0.016 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.1, 134.1, 130.9, 129.1, 125.1, 113.7, 76.5, 72.6, 72.3, 68.4, 55.3, 39.1, 38.7, 26.1, 18.4, 14.9, 14.3, -3.9, -4.0; high resolution mass spectrum (CI, NH_3) m/z 487.1873 [$(M+H)^+$; calcd for $C_{23}H_{40}O_4BrSi$: 487.1879].

Anal. Calcd for $C_{23}H_{39}O_4BrSi$: C, 56.66; H, 8.06. Found: C, 56.72; H, 8.07.

EXAMPLE 15

Mesylate (-)-21.

A solution of alcohol (-)-**20** (6.85 g, 14.1 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C and MsCl (2.20 mL, 28.4 mmol) was added over 2 min. After 10 min, the reaction was quenched with aqueous $NaHSO_4$ (1.0 M, 100 mL). The organic

phase was washed with water (100 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (10% ethyl acetate/hexane) afforded (-)-**21** (7.85 g, 99% yield) as a colorless oil: $[\alpha]^{23}_D$ -14.6° © 1.40, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2960 (s), 2940 (s), 2880 (m), 2860 (s), 1730 (w), 1610 (m), 1583 (m), 1510 (s), 1460 (m), 1410 (m), 1362 (s), 1300 (m), 1250 (s), 1220 (s), 1175 (s), 1080 (s), 1032 (s), 1002 (m), 960 (m), 937 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.23 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 6.07 (d, J = 9.4 Hz, 1 H), 4.74 (d, J = 0.4 Hz, 2 H), 4.38 (ABq, J_{AB} = 11.7 Hz, $\Delta\delta_{AB}$ = 25.5 Hz, 2 H), 3.79 (s, 3 H), 3.61 (apparent t, J = 5.2 Hz, 1 H), 3.44 (dd, J = 9.2, 5.7 Hz, 1 H), 3.22 (dd, J = 9.2, 7.3 Hz, 1 H), 3.01 (s, 3 H), 2.84-2.77 (m, 1 H), 1.99-1.91 (m, 1 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.1, 140.9, 130.8, 129.1, 116.7, 113.8, 76.1, 74.2, 72.6, 72.1, 55.3, 39.6, 38.8, 38.5, 26.0, 18.3, 14.7, 14.3, -3.9, -4.0; high resolution mass spectrum (CI, NH_3) m/z 582.1911 [$(M+NH_4)^+$; calcd for $C_{24}H_{45}NO_6BrSSi$: 582.1920].

EXAMPLE 16

Vinyl Bromide (-)-22.

A solution of mesylate (-)-**21** (6.43 g, 11.4 mmol) in benzene (120 mL) was treated with $LiBHEt_3$ (1.0 M in THF, 25.0 mL, 25.0 mmol) at room temperature. After 0.5 h, the reaction was quenched with aqueous NaOH (1.0 N, 50 mL). The mixture was diluted with ethyl acetate (200 mL), washed with brine (2 x 200 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% ethyl acetate/hexane) provided (-)-**22** (4.86 g, 91%) as a colorless oil: $[\alpha]^{23}_D$ -16.9° © 1.69, $CHCl_3$); IR ($CHCl_3$) 3005 (m), 2965 (s), 2935 (s), 2860 (s), 1660 (w), 1610 (m), 1585 (w), 1510 (m), 1460 (m), 1425 (w), 1377 (m), 1360 (m), 1300 (m), 1250

(s), 1180 (m), 1170 (m), 1075 (s), 1030 (m), 860 (m), 835 (s), 805 (m), 660 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.24 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.47 (apparent dd, J = 9.0, 1.2 Hz, 1 H), 4.39 (ABq, J_{AB} = 11.7 Hz, $\Delta\delta_{AB}$ = 15.8 Hz, 2 H), 3.79 (s, 3 H), 3.56 (apparent t, J = 5.4 Hz, 1 H), 3.50 (dd, J = 9.1, 5.1 Hz, 1 H), 3.22 (dd, J = 8.8, 8.1 Hz, 1 H), 2.74-2.67 (m, 1 H), 2.21 (d, J = 1.1 Hz, 3 H), 1.99-1.91 (m, 1 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.1, 133.4, 131.0, 129.1, 120.6, 113.7, 76.7, 72.6, 72.5, 55.3, 39.7, 38.7, 28.8, 26.1, 18.4, 14.8, 14.4, -3.96, -4.01; high resolution mass spectrum (FAB, NBA) *m/z* 493.1763 [$(M+Na)^+$; calcd for $C_{23}H_{39}O_3BrSiNa$: 493.1750].

EXAMPLE 17

Vinyl Silane (-)-23.

A solution of vinyl bromide (-)-**22** (83.2 mg, 0.177 mmol) in THF (2.0 mL) was cooled to -78 °C and *n*-BuLi (1.6 M in hexane, 260 ml, 416 mmol) was added over 10 min. After 1 h at -78 °C and 15 min at room temperature, the reaction was quenched with H_2O (200 mL). The mixture was concentrated and dissolved in ethyl acetate (30 mL), washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% ethyl acetate/hexane) provided (-)-**23** (47.9 mg, 69% yield) as a colorless oil: $[\alpha]^{23}_D$ -61.5° © 0.615, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3470 (m, br), 1614 (m), 1588 (w), 1513 (s), 1465 (m), 1442 (m), 1415 (m), 1360 (m), 1302 (m), 1250 (s), 1176 (m), 1120 (m), 1077 (m), 1032 (m), 992 (m), 830 (s), 820 (s), 805 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.22 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 6.22 (dq, J = 10.5, 1.6 Hz, 1 H), 4.42 (ABq, J_{AB} = 11.4 Hz, $\Delta\delta_{AB}$ = 18.8 Hz, 2 H), 3.78 (s, 3 H), 3.65 (br s, 1 H), 3.56 (dd, J = 9.1, 4.0 Hz, 1 H), 3.44 (dd, J = 8.8, 2.9 Hz,

1 H), 3.42 (apparent t, *J* = 8.8 Hz, 1 H), 2.45 (dqd, *J* = 10.3, 6.6, 2.7 Hz, 1 H), 1.95-1.87 (m, 1 H), 1.78 (d, *J* = 1.6 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.80 (d, *J* = 7.0 Hz, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.4, 147.7, 130.8, 129.7, 129.4, 113.9, 79.9, 76.4, 73.3, 55.3, 38.1, 36.3, 27.1, 26.6, 17.8, 13.4, 13.1, -3.4, -3.7; high resolution mass spectrum (CI, NH_3) *m/z* 393.2821 [$(M+H)^+$; calcd for $C_{23}H_{41}O_3Si$: 393.2824].

Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.36; H, 10.27. Found: C, 70.58; H, 10.57.

EXAMPLE 18

***trans* Olefin (+)-24.**

A solution of vinyl bromide (-)-**22** (27.8 mg, 0.0591 mmol) in ether (600 μL) was cooled to - 78 °C, and *t*-BuLi (1.7 M in pentane, 103 μL, 0.175 mmol) was added over 2 min. After 10 min at -78 °C and 5 min at room temperature, the reaction was quenched with MeOH (100 mL). The mixture was filtered through a short silica plug, and concentrated. Flash chromatography (1% ethyl acetate/hexane) provided (+)-**24** (21.9 mg, 94% yield) as a colorless oil; $[\alpha]^{23}_D$ +19.3° © 1.10, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2960 (s), 2935 (s), 2880 (m), 2860 (s), 1612 (m), 1587 (w), 1510 (s), 1462 (m), 1440 (m), 1405 (w), 1375 (m), 1360 (m), 1300 (m), 1250 (s), 1170 (m), 1090 (s), 1034 (s), 1002 (m), 970 (m), 934 (w), 850 (m), 832 (s), 720 (m) cm^{-1}; ^1H NMR (500 MHZ, C_6D_6) d 7.24 (d, *J* = 8.7 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 5.43 (ddq, *J* = 15.3, 7.8, 1.4 Hz, 1 H), 5.34 (dqd, *J* = 15.4, 6.3, 0.7 Hz, 1 H), 4.38 (ABq, J_{AB} = 11.7 Hz, $\Delta\delta_{AB}$ = 30.7 Hz, 2 H), 3.58 (apparent t, *J* = 5.2 Hz, 1 H), 3.57 (dd, *J* = 9.0, 5.1 Hz, 1 H), 3.36 (dd, *J* = 9.0, 7.2 Hz, 1 H), 3.30 (s, 3 H), 2.39 (ddq, *J* = 6.8, 6.8, 6.8 Hz, 1 H), 2.17-2.10 (m, 1 H), 1.58 (apparent d, *J* = 6.1 Hz, 3 H), 1.07 (d, *J* = 7.2 Hz, 3 H),

1.05 (d, J = 6.9 Hz, 3 H), 1.00 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.0, 135.6, 131.1, 129.1, 123.9, 113.7, 78.4, 72.6, 72.5, 55.3, 40.4, 37.9, 26.2, 26.1, 18.4, 18.0, 15.9, 15.1, -3.8, -4.1; high resolution mass spectrum (CI, NH_3) m/z 393.2836 [$(M+H)^+$; calcd for $C_{23}H_{41}O_3Si$: 393.2824].

EXAMPLE 19

Alcohol (-)-25.

A solution of PMB ether (-)-**22** (50.0 mg, 0.106 mmol) and PMB acetal (-)-**15** (46.5 mg, 0.106 mmol) in CH_2Cl_2 (2.0 mL) was cooled to 0 °C, then treated with H_2O (100 mL) and DDQ (26.5 mg, 0.117 mmol). After 30 min, the mixture was diluted with ether (60 mL), washed with saturated aqueous $NaHCO_3$ (60 mL), brine (3 X 60 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (gradient elution, 5% -> 10% ethyl acetate/hexane) afforded (-)-**25** (31.0 mg, 83% yield) and recovered (-)-**15** (40.0 mg, 86% recovery).

(-)-**25**: $[\alpha]^{23}_D$ -13.3° © 0.99, $CHCl_3$); IR ($CHCl_3$) 3640 (w), 3520 (m), 3000 (m), 2960 (s), 2940 (s), 2890 (m), 2860 (s), 1660 (w), 1472 (m), 1465 (m), 1440 (m), 1407 (m), 1390 (m), 1380 (m), 1360 (m), 1258 (s), 1072 (s), 1023 (s), 1005 (s), 980 (m), 937 (m), 847 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 5.50 (apparent dd, J = 9.0, 1.1 Hz, 1 H), 3.65 (dd, J = 11.0, 4.8 Hz, 1 H), 3.59 (dd, J = 11.0, 5.7 Hz, 1 H), 3.56 (apparent t, J = 5.2 Hz, 1 H), 2.80- 2.72 (m,1 H), 2.25 (d, J = 1.0 Hz, 3 H), 2.20 (br s, 1 H),1.86-1.78 (m, 1 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 132.6, 121.7, 79.7, 65.6, 40.9, 38.8, 28.9, 26.1, 18.3, 15.5, 15.0, -3.9, -4.0; high resolution mass spectrum (CI, NH_3) m/z 351.1087 [M^+; calcd for $C_{15}H_{31}O_2BrSi$: 351.1093].

EXAMPLE 20

Alcohol (+)-26.

A solution of amide (+)-**17** (323.5 mg, 0.738 mmol) in EtOH (8.0 mL) was stirred for 5 h under H_2 atmosphere in the presence of Pearlman's catalyst (20% $Pd(OH)_2/C$, 104.1 mg), then filtered and concentrated. Flash chromatography (10 mL silica, 20% ethyl acetate/hexane) provided (+)-**26** (216.7 mg, 92% yield) as a colorless oil: $[\alpha]^{23}_D$ +16.1° © 2.60, $CHCl_3$); IR ($CHCl_3$) 3480 (m, br), 3000 (s), 2958 (s), 2935 (s), 2880 (s), 2860 (s), 1635 (s), 1460 (s), 1415 (m), 1390 (s), 1360 (m), 1285 (w), 1255 (s), 1174 (m), 1148 (m), 1093 (s), 1070 (s), 1047 (s), 1033 (s), 990 (s), 935 (m), 905 (w), 860 (s), 830 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 4.05 (dd, J = 9.1, 3.1 Hz, 1 H), 3.69 (s, 3 H), 3.55-3.50 (m, 1 H), 3.23 (ddd, J = 10.1, 10.1, 2.8 Hz, 1 H), 3.13 (s, 3 H), 3.09 (br m, 1 H), 2.81 (br m, 1 H), 1.91-1.83 (m, 1 H), 1.14 (d, J = 7.0 Hz, 3 H), 0.879 (d, J = 7.0 Hz, 3 H), 0.879 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 177.3, 75.2, 64.9, 61.5, 40.8, 38.2, 32.2, 26.0, 18.2, 15.9, 12.8, -4.1, -4.3; high resolution mass spectrum (CI, NH_3) *m/z* 320.2265 [$(M+H)^+$; calcd for $C_{15}H_{34}NO_4Si$: 320.2256].

EXAMPLE 21

Aldehyde (+)-27.

A solution of alcohol (+)-**26** (8.80 g, 27.5 mmol) and NEt_3 (15.3 mL, 110 mmol) in CH_2Cl_2 (50 mL) was cooled to -10 °C and treated with SO_3.pyr (13.1 g, 82.6 mmol) in DMSO (100 mL). After 20 min at room temperature, the mixture was diluted with ether (300 mL), washed with aqueous $NaHSO_4$ (1.0 M, 200 mL), brine (4 x 200 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (20% ethyl acetate/hexane) afforded (+)-**27** (8.55 g, 98% yield) as a colorless oil: $[\alpha]^{23}_D$ +51.2° © 1.00, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2960 (s), 2940 (s), 2895 (m), 2865 (m), 1750 (m), 1720

(s), 1647 (s), 1460 (s), 1420 (m), 1390 (s), 1360 (m), 1255 (s), 1180 (m), 1105 (m), 1077 (m), 1040 (s), 995 (s), 936 (m), 853 (s), 837 (s), 710 (m), 657 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 9.68 (d, J = 1.6 Hz, 1 H), 4.22 (dd, J = 8.9, 2.6 Hz, 1 H), 3.68 (s, 3 H), 3.10 (apparent s, 4 H), 2.46 (qdd, J = 7.1, 2.6, 1.5 Hz, 1 H), 1.16 (d, J = 6.9 Hz, 3 H), 1.10 (d, J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.092 (s, 3 H), 0.088 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 203.2, 175.6, 75.1, 61.5, 52.1, 39.6, 32.1, 25.9, 18.2, 15.4, 10.2, -4.07, -4.11; high resolution mass spectrum (CI,NH_3) m/z 318.2096 [$(M+H)^+$; $C_{15}H_{32}NO_4Si$: 318.2100].

EXAMPLE 22

Dithiane (+)-28.

A solution of $ZnCl_2$ (dried at 140 °C for 1 h under vacuum, 170.5 mg, 1.25 mmol) in ether (6.0 mL) was cooled to 0 °C and $(TMSSCH_2)_2CH_2$ (175.0 μL, 0.628 mmol) was added. The resultant white milky suspension was treated with aldehyde (+)-**27** (180.0 mg, 0.567 mmol) in ether (6.0 mL). The mixture was stirred for 4.5 h at 0 °C and 1.5 h at room temperature, then partitioned between ethyl acetate (50 mL) and aqueous ammonia (30 mL). The organic phase was washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) provided (+)-**28** (182.9 mg, 79% yield) as a white solid: mp 55-57 °C; $[\alpha]^{23}_D$ +18.5° © 1.44, $CHCl_3$); IR ($CHCl_3$) 3015 (m), 2970 (s), 2945 (s), 2910 (m), 2870 (m), 1665 (s), 1475 (m), 1470 (m), 1437 (m), 1430 (m), 1420 (m), 1390 (m), 1365 (m), 1320 (w), 1280 (m), 1260 (m), 1120 (m), 1115 (m), 1097 (m), 1080 (m), 1065 (m), 1040 (m), 1000 (m), 940 (w), 925 (w), 910 (w), 877 (m), 838 (s), 815 (m), 800 (m), 700 (w), 675 (w), 660 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 4.33 (d, J = 4.2 Hz, 1 H), 4.23 (dd, J = 7.1, 3.6 Hz, 1 H), 3.68 (s, 3 H), 3.15 (s, 3 H), 2.98 (dq, J = 6.8, 3.7 Hz, 1 H), 2.90 (ddd, J = 14.1, 12.2, 2.5 Hz, 1 H), 2.83-2.77 (m, 3

H), 2.09-2.03 (m, 1 H), 1.94 (ddq, J = 7.2, 7.2, 4.3 Hz, 1 H), 1.88-1.76 (m, 1 H), 1.08 (d, J = 7.2 Hz, 3 H), 1.07 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 176.2, 73.2, 61.0, 50.8, 44.2, 38.6, 31.3, 30.3, 26.2, 18.4, 12.9, 11.0, -4.1, -4.2; high resolution mass spectrum (CI, NH_3) m/z 408.2081 [$(M+H)^+$; calcd for $C_{18}H_{38}NO_3S_2Si$: 408.2062].

Anal. Calcd. for $C_{18}H_{37}NO_3S_2Si$: C, 53.03; H, 9.15. Found: C, 53.06; H, 9.31.

EXAMPLE 23

Aldehyde (+)-29.

A solution of dithiane (+)-**28** (1.05 g, 2.58 mmol) in THF (40 mL) was cooled to -78 °C and DIBAL (1.0 M in hexane, 5.15 mL, 5.15 mmol) was added over 15 min. After 10 min at -78 °C, the mixture was quenched with MeOH (2.0 mL) and partitioned between ether and saturated aqueous Rochelle's salt (50 mL each). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) provided (+)-**29** (822 mg, 91% yield) as white solid: mp 54-55 °C; $[\alpha]^{23}_D$ +50.8° © 1.19, $CHCl_3$); IR ($CHCl_3$) 2965 (s), 2940 (s), 2910 (s), 2865 (s), 2720 (w), 1730 (s), 1475 (m), 1467 (m), 1428 (m), 1418 (m), 1390 (m), 1365 (m), 1280 (m), 1260 (s), 1190 (m), 1150 (m), 1104 (s), 1070 (m), 1030 (s), 1007 (m), 953 (m), 940 (m), 910 (m), 835 (s), 810 (m), 675 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 9.70 (s, 1 H), 4.44 (dd, J = 8.3, 2.2 Hz, 1 H), 4.38 (d, J = 3.7 Hz, 1 H), 2.93 (ddd, J = 14.1, 12.3, 2.6 Hz, 1 H), 2.84-2.80 (m, 3 H), 2.43 (qd, J = 7.1, 2.2 Hz, 1 H), 2.13-2.07 (m, 1 H), 2.02 (dqd, J = 8.2, 7.1, 3.7 Hz, 1 H), 1.88-1.79 (m, 1 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.05 (d, J = 7.1 Hz, 3 H), 0.87 (s, 9 H), 0.16 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 204.6, 71.1, 51.0, 49.7, 43.5, 31.3, 30.3, 26.2, 26.0, 18.4,

12.9, 6.8, -3.9, -4.3; high resolution mass spectrum (CI, NH_3) *m/z* 349.1678 [$(M+H)^+$; calcd for $C_{16}H_{33}O_2S_2Si$: 349.1691].

Anal. Calcd for $C_{16}H_{32}O_2S_2Si$: C,55.12; H, 9.25. Found: C, 55.08; H, 9.28.

EXAMPLE 24

Dimethoxy Acetal (+)-30.

A solution of aldehyde (+)-**29** (792 mg, 2.27mmol) in $HC(OMe)_3$/MeOH (48 mL, 1:5) was treated with $TsOH{\cdot}H_2O$ (8.6 mg, 0.045 mmol) at room temperature. After 30 min, NEt_3 (1.0 mL) was added and the mixture was concentrated. Flash chromatography (10% ethyl acetate/hexane) provided (+)-**30** (886 mg, 99% yield) as a white solid: mp 58-59 °C; $[\alpha]^{23}_D$ +27.1° © 2.85, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2940 (s), 2905 (s), 2860 (m), 2835 (m), 1473 (m), 1463 (m), 1432 (m), 1425 (m), 1415 (m), 1387 (m), 1362 (m), 1340 (w), 1278 (m), 1252 (s), 1190 (m), 1158 (m), 1104 (s), 1070 (m), 1050 (m), 1030 (s), 1005 (m), 963 (m), 938 (m), 908 (m), 873 (m), 834 (s), 810 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 4.41 (d, J = 3.1 Hz, 1 H), 4.23 (d, J = 8.6 Hz, 1 H), 4.02 (dd, J = 8.6, 1.3 Hz, 1 H), 3.29 (s, 3 H), 3.26 (s, 3 H), 2.93 (ddd, J = 14.0, 12.4, 2.5 Hz, 1 H), 2.85-2.78 (m, 3 H), 2.11-2.05 (m, 1 H), 1.93-1.77 (m, 3 H), 1.00 (d, J = 7.2 Hz, 3 H), 0.91 (s, 9 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.17 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 105.0, 71.5, 53.0, 51.5, 51.2, 43.8, 37.4, 31.3, 30.2, 26.3, 18.8, 12.9, 8.1, -3.8, -4.3; high resolution mass spectrum (FAB, NBA) *m/z* 417.1934 [$(M+Na)^+$; calcd for $C_{18}H_{38}O_3S_2SiNa$: 417.1930].

Anal. Calcd for $C_{18}H_{38}O_3S_2Si$: C, 54.78; H, 9.70. Found: C, 54.80; H, 9.66.

EXAMPLE 25

Hydroxy Acetal (-)-32.

A solution of dithiane (+)-**30** (3.60 g, 9.12 mmol)

in 10% HMPA/THF (60 mL) was cooled to -78 °C and treated with *t*-BuLi (1.7 M in pentane, 5.63 mL, 9.58 mmol) dropwise over 15 min. The mixture was stirred 1 h at -78 °C and 1 h at -42 °C, then recooled to -78 °C. A solution of benzyl *R*-(-)-glycidyl ether (1.65 g, 10.0 mmol) in 10% HMPA/THF (12 mL) was added via cannula. After 0.5 h, the reaction mixture was warmed to -42 °C for 0.5 h and quenched with saturated aqueous NH_4Cl (20 mL). The mixture was diluted with ether (200 mL), washed with water, brine (200 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) afforded (-)-**32** (4.04 g, 79% yield) as a colorless oil: $[\alpha]^{23}_D$ -5.9° © 2.1, $CHCl_3$); IR ($CHCl_3$) 3450 (w, br), 3020 (m), 2960 (s), 2940 (s), 2910 (m), 2860 (m), 2840 (m), 1605 (w), 1500 (w), 1475 (m), 1468 (m), 1458 (m), 1440 (m), 1430 (m), 1393 (m), 1387 (m), 1365 (m), 1280 (w), 1255 (m), 1233 (m), 1203 (m), 1167 (w), 1153 (w), 1110 (s), 1060 (m), 1045 (m), 1030 (m), 1010 (m), 980 (w), 940 (m), 910 (w), 860 (m), 837 (s), 800 (m), 695 (m), 670 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.35-7.25 (m, 5 H), 4.64 (dd, J = 4.0, 1.1 Hz, 1 H), 4.57 (ABq, J_{AB} = 12.1 Hz, $\Delta\delta_{AB}$ = 17.8 Hz, 2 H), 4.21 (d, J = 7.7 Hz, 1 H), 4.14-4.09 (m, 1 H), 3.48 (dd, J = 9.5, 6.0 Hz, 1 H), 3.47 (dd, J = 9.6, 5.0 Hz, 1 H), 3.37 (d, J = 0.7 Hz, 1 H), 3.36 (s, 3 H), 3.29 (s, 3 H), 3.08 (ddd, J = 14.4, 11.4, 2.9 Hz, 1 H), 2.95 (ddd, J = 14.4, 11.3, 3.1 Hz, 1 H), 2.71-2.64 (m, 2 H), 2.59 (dqd, J = 6.7, 6.7, 0.9 Hz, 1 H), 2.49 (dd, J = 15.6, 7.9 Hz, 1 H), 2.30 (dq, J = 4.0, 7.3 Hz, 1 H), 2.27 (dd, J = 15.6, 2.3 Hz, 1 H), 2.04-2.00 (m, 1 H), 1.86-1.78 (m, 1 H), 1.18 (d, J = 7.4 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 138.2, 128.4, 127.6, 106.9, 74.4, 73.3, 70.0, 67.9, 55.7, 53.6, 52.6, 47.2, 39.4, 38.5, 26.3, 26.1, 26.0, 25.0, 18.3, 9.8, 9.5, -3.9, -4.9; high resolution mass spectrum (FAB, NBA) m/z 581.2763 [$(M+Na)^+$;

calcd for $C_{28}H_{50}O_5S_2SiNa$: 581.2767].

EXAMPLE 26

Ketone (+)-33.

A solution of hydroxy acetal (-)-**32** (3.94 g, 7.05 mmol) in H_2O/MeOH (1:9, 75 mL) was treated with $(CF_3CO_2)_2IPh$ (4.55 g, 10.6 mmol) at 0 °C. After 5 min, the mixture was quenched with saturated $NaHCO_3$ (20 mL) and extracted with ether (200 mL). The organic phase was washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (20% ethyl acetate/hexane) furnished (+)-**33** (2.66 g, 80% yield) as a colorless oil. $[\alpha]^{23}_D$ +36° © 0.36, $CHCl_3$); IR ($CHCl_3$) 3580 (w, br), 3005 (m), 2960 (s), 2930 (s), 2900 (m), 2860 (m), 1710 (m), 1463 (m), 1455 (m), 1387 (m), 1362 (m), 1253 (m), 1220 (m), 1105 (s), 1070 (s),1053 (s), 1030 (s), 1002 (m), 938 (m), 866 (m), 830 (s), 808 (m), 690 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.34-7.25 (m, 5 H), 4.54 (apparent s, 2 H), 4.40-4.25 (m, 1 H), 4.23 (dd, J = 7.6, 1.9 Hz, 1 H), 4.19 (d, J = 8.0 Hz, 1 H), 3.46 (dd, J = 9.7, 4.9 Hz, 1 H), 3.43 (dd, J = 9.7, 5.9 Hz, 1 H), 3.27 (s, 3 H), 3.25 (s, 3 H), 3.01 (d, J = 3.8 Hz, 1 H), 2.76 (dd, J = 18.0, 8.7 Hz, 1 H), 2.74 (dq, J = 7.1, 7.1 Hz, 1 H), 2.62 (dd, J = 17.9, 3.2 Hz, 1 H), 1.83 (dqd, J = 8.0, 7.0, 1.9 Hz, 1 H), 0.97 (d, J = 7.1 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.83 (s, 9 H), 0.06 (s, 3 H), -0.05 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 213.0, 138.0, 128.4, 127.71, 127.68, 105.0, 73.4, 73.3, 71.8, 66.5, 52.9, 52.6, 52.3, 46.5, 37.9, 26.1, 18.4, 12.7, 8.8, -4.1, -4.8; high resolution mass spectrum (FAB, NBA) *m/z* 491.2821 [$(M+Na)^+$; calcd for $C_{25}H_{44}O_6SiNa$: 491.2805].

EXAMPLE 27

Diol (-)-34.

A solution of $Me_4NBH(OAc)_3$ (1.80 g, 6.84 mmol) in $HOAc/CH_3CN$ (1:1, 10.0 mL) was cooled to -40 °C and ketone (+)-**33** (536 mg, 1.14 mmol) in CH_3CN (5 mL) was added. After 12 h at -20 °C, the mixture was treated with saturated aqueous Rochelle's salt (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$, brine (100 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (1:1:1, CH_2Cl_2/ether/hexane) provided (-)-**34** (519 mg, 97% yield) as a colorless oil: $[\alpha]^{23}_D$ -7.78° © 0.900, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3460 (m, br), 3015 (m), 2960 (s), 2940 (s), 2900 (m), 2865 (s), 1470 (m), 1460 (m),1390 (m), 1365 (m), 1260 (m), 1230 (m), 1208 (m), 1112 (s), 1065 (s), 1030 (m), 1010 (m), 942 (m), 865 (m), 838 (m), 698 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.33-7.30 (m, 4 H), 7.29-7.25 (m, 1 H), 4.55 (ABq, J_{AB} = 12.0 Hz, $\Delta\delta_{AB}$ = 15.7 Hz, 2 H), 4.16-4.11 (m, 1 H), 4.13 (d, J = 7.8 Hz, 1 H), 4.07 (dd, J = 4.8, 1.6 Hz, 1 H), 3.73 (br s, 1 H), 3.68 (dddd, J = 9.3, 9.3, 2.4, 2.4 Hz, 1H), 3.50 (dd, J = 9.6, 4.5 Hz, 1 H), 3.42 (dd, J = 9.4, 7.0 Hz, 1 H), 3.38 (s, 3 H), 3.29 (s, 3 H), 3.09 (d, J = 4.0 Hz, 1 H), 1.90 (dqd, J = 7.0, 7.0, 1.5 Hz, 1 H), 1.76 (br dd, J = 13.6, 8.5 Hz, 1 H), 1.68 (dqd, J = 9.6, 6.9, 5.0 Hz, 1 H), 1.49 (ddd, J = 14.3, 9.0, 2.9 Hz, 1 H), 0.894 (d, J = 7.9 Hz, 3 H), 0.886 (s, 9 H), 0.80 (d, J = 7.0 Hz, 3 H), 0.055 (s, 3 H), 0.048 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 138.2, 128.4, 127.7, 127.6, 107.3, 74.5, 73.3, 71.0, 70.9, 67.8, 55.2, 52.1, 45.9, 37.3, 36.9, 25.9, 18.2, 11.6, 10.6, -4.3, -4.7; high resolution mass spectrum (FAB, NBA) *m/z* 493.2951 [$(M+Na)^+$; calcd for $C_{25}H_{46}O_6SiNa$: 493.2962].

EXAMPLE 28

Alcohol (-)-35.

A solution of (-)-**34** (123.3 mg, 0.262 mmol) in benzene (10 mL) was treated with $TsOH \cdot H_2O$ (2.0 mg, 0.0105 mmol) at room temperature. After 20 min, the mixture was quenched with NEt_3 (1.0 mL) and concentrated. Flash chromatography (2% ether/CH_2Cl_2) afforded **35** (100.1 mg, β/α = 2:1, 87% yield) as a colorless oil.

β Anomer (**35**): $[\alpha]^{23}_D$ -3.3° © 2.25, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3580 (w), 3490 (w), 3010 (m), 2960 (s), 2930 (s), 2880 (m), 2860 (s), 1603 (w), 1525 (w), 1515 (w), 1493 (m), 1470 (m), 1460 (m), 1450 (m), 1387 (m), 1360 (m), 1347 (m), 1330 (m), 1253 (s), 1225 (m), 1200 (m), 1143 (m), 1110 (s), 1070 (s), 1045 (s), 1020 (s), 1015 (m), 1003 (m), 985 (m), 950 (m), 870 (m), 853 (m), 833 (s), 807 (m), 800 (m), 790 (m), 690 (m), 670 (m), 657 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.34-7.25 (m, 5 H), 4.69 (d, J = 2.4 Hz, 1 H), 4.55 (ABq, J_{AB} = 12.0 Hz, $\Delta\delta_{AB}$ = 14.6 Hz, 2 H), 4.17-4.12 (m, 1 H), 3.78 (ddd, J = 9.7, 9.7, 2.5 Hz, 1 H), 3.60 (apparent t, J = 2.7 Hz, 1 H), 3.51 (dd, J = 9.5, 4.1 Hz, 1 H), 3.42 (s, 3 H), 3.39 (dd, J = 9.5, 7.0 Hz, 1 H), 2.86 (d, J = 3.8 Hz, 1 H), 1.88 (apparent qt, J = 7.1, 2.7 Hz, 1 H), 1.76 (ddd, J = 14.4, 8.9, 2.6 Hz, 1 H), 1.72-1.65 (m, 1 H), 1.53 (ddd, J = 14.4, 9.3, 2.9 Hz, 1 H), 0.90 (d, J = 8.2 Hz, 3 H), 0.89 (s, 9 H), 0.78 (d, J = 6.8 Hz, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 138.2, 128.4, 127.7, 101.2, 76.7, 74.7, 73.3, 73.0, 67.4, 56.6, 41.1, 36.0, 34.7, 25.9, 18.1, 13.7, 9.7, -4.6, -4.9; high resolution mass spectrum (FAB, NBA) m/z 461.2693 [$(M+Na)^+$; calcd for $C_{24}H_{42}O_5SiNa$: 461.2699].

α Anomer (**35**): $[\alpha]^{23}_D$ +48° © 0.54, $CHCl_3$); IR ($CHCl_3$) 3670 (w), 3570 (w), 3480 (w, br), 3005 (m), 2960 (s), 2930 (s), 2880 (m), 2855 (s), 1600 (w), 1527 (w), 1515 (w),

1495 (w), 1460 (m), 1360 (m), 1253 (s), 1225 (m), 1212 (m), 1200 (m), 1170 (m), 1148 (m), 1106 (s), 1087 (s), 1048 (s), 1030 (s), 963 (m), 872 (m), 833 (s), 788 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.34-7.24 (m, 5 H), 4.55 (ABq, J_{AB} = 12.1 Hz, $\Delta\delta_{AB}$ = 14.4 Hz, 2 H), 4.30 (d, J = 2.9 Hz, 1 H), 4.12-4.07 (m, 1 H), 4.01 (ddd, J = 9.2, 9.2, 2.7 Hz, 1 H), 3.51 (apparent t, J = 4.4 Hz, 1 H), 3.50 (dd, J = 9.5, 4.2 Hz, 1 H), 3.39 (dd, J = 9.5, 7.1 Hz, 1 H), 3.28 (s, 3 H), 2.86 (d, J = 3.2 Hz, 1 H), 1.85 (qdd, J = 7.3, 5.2, 2.9 Hz, 1 H), 1.76 (dqd, J = 9.3, 6.9, 4.0 Hz, 1 H), 1.71 (ddd, J = 14.5, 9.0, 2.8 Hz, 1 H), 1.55 (ddd, J = 14.4, 9.2, 2.9 Hz, 1 H), 0.96 (d, J = 7.3 Hz, 3 H), 0.88 (s, 9 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.03 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR d 138.2, 128.4, 127.7, 101.2, 76.7, 74.7, 73.3, 73.0, 67.4, 56.7, 41.1, 36.0, 34.7, 25.9, 18.1, 13.7, 9.7, -4.6, -4.9; high resolution mass spectrum (FAB, NBA) m/z 461.2715 [$(M+Na)^+$; calcd for $C_{24}H_{42}O_5SiNa$: 461.2699].

EXAMPLE 29

Methyl Pyranoside 36.

A solution of **35** (281.2 mg, β/α = 2:1, 0.642 mmol) and 2,6-lutidine (224.0 μL, 1.92 mmol) in CH_2Cl_2 (6.0 mL) was cooled to 0 °C and TBSOTf (295.0 μL, 1.28 mmol) was added over 5 min. After 1 h at 0 °C, the mixture was diluted with ethyl acetate (100 mL), washed with aqueous $NaHSO_4$ (1.0 M, 50 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% ethyl acetate/hexane) provided **36** (344.6 mg, β/α = 2:1, 97% yield) as a colorless oil.

α anomer: $[\alpha]^{23}_D$ +50.0° © 1.44, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2935 (s), 2885 (s), 2860 (s), 1490 (w), 1460 (m), 1388 (m), 1378 (m), 1360 (m), 1250 (s), 1190 (m), 1145 (m), 1105 (s), 1085 (s), 1050 (s), 1025 (s), 1002 (s), 963 (m), 934 (m), 867 (m), 833 (s), 690 (m) cm^{-1}; ^1H NMR (500 MHZ,

$CDCl_3$) d 7.32-7.25 (m, 5 H), 4.51 (ABq, J_{AB} = 12.1 Hz, $\Delta\delta_{AB}$ = 19.7 Hz, 2 H), 4.23 (d, J = 4.8 Hz, 1 H), 4.03 (dddd, J = 8.0, 5.3, 5.3, 2.5 Hz, 1 H), 3.87 (ddd, J = 9.9, 7.8, 1.8 Hz, 1 H), 3.53 (dd, J = 7.2, 4.8 Hz, 1 H), 3.39 (dd, J = 9.8, 5.6 Hz, 1 H), 3.37 (dd, J = 10.0, 5.2 Hz, 1 H), 3.33 (s, 3 H), 1.79 (dqd, J = 7.1, 7.1, 4.9 Hz, 1 H), 1.71-1.64 (m, 2 H), 1.53 (ddd, J = 14.4, 8.8, 1.9 Hz, 1 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.865 (s, 9 H), 0.862 (d, J = 6.9 Hz, 3 H), 0.07 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H), 0.005 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 138.5, 128.3, 127.6, 127.5, 103.8, 75.5, 73.2, 72.8, 69.8, 69.1, 55.7, 38.9, 38.5, 37.6, 26.0, 25.8, 18.18, 18.16, 15.1, 12.9, -3.9, -4.6, -4.7, -4.8; high resolution mass spectrum (FAB, NBA) m/z 575.3552 [$(M+Na)^+$; calcd for $C_{30}H_{56}O_5Si_2Na$: 575.3564].

β anomer: $[\alpha]^{23}_D$ +13.3° © 1.38, $CHCl_3$); IR ($CHCl_3$) 3003 (m), 2960 (s), 2935 (s), 2880 (s), 2860 (s), 1495 (w), 1470 (m), 1464 (m), 1390 (m), 1360 (m), 1350 (m), 1330 (w), 1253 (s), 1155 (s), 1140 (s), 1120 (s), 1090 (s), 1045 (s), 1022 (s), 1002 (s), 953 (m), 933 (m), 850 (s), 830 (s), 690 (m), 658 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.32-7.22 (m, 5 H), 4.74 (d, J = 2.4 Hz, 1 H), 4.50 (ABq, J_{AB} = 13.2 Hz, $\Delta\delta_{AB}$ = 17.8 Hz, 2 H), 4.23-4.18 (m, 1 H), 3.74 (ddd, J = 10.6, 10.6, 1.3 Hz, 1 H), 3.60 (apparent t, J = 2.7 Hz, 1 H), 3.48 (s, 3 H), 3.38 (dd, J = 9.8, 4.5 Hz, 1 H), 3.35 (dd, J = 9.8, 5.7 Hz, 1 H), 1.88 (qdd, J = 7.1, 2.7, 2.7 Hz, 1 H), 1.66 (ddd, J = 14.0, 10.1, 1.6 Hz, 1 H), 1.63-1.55 (m, 1 H), 1.49 (ddd, J = 14.0, 10.8, 1.8 Hz, 1 H), 0.91 (d, J = 7.1 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.785 (d, J = 6.8 Hz, 3 H), 0.07 (s, 3 H), 0.045 (s, 3 H), 0.040 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 138.5, 128.2, 127.6, 127.4, 100.6, 76.9, 75.8, 73.2, 71.7, 67.9, 56.7, 41.1, 38.4, 35.0, 26.1, 25.8, 18.2, 18.1, 14.0, 9.7, -3.9, -4.5, -5.0; high resolution mass spectrum (FAB, NBA) m/z 575.3560

[(M+Na)$^+$; calcd for $C_{30}H_{56}O_5Si_2Na$: 575.3564].

EXAMPLE 30

Primary Alcohol 37.

A solution of **36** (331.6 mg, 0.600 mmol) in EtOH/EtOAc (1:8, 9 mL) was treated with Pd/C (10% wet, E101 NE/W, 51.2 mg) under H_2 atmosphere for 3 h, then filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) provided **37** (276.6 mg, β/α = 2:1, 99% yield) as a colorless oil.

β anomer: $[\alpha]^{23}_D$ +16.9° © 2.52, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3590 (w, br), 3450 (w, br), 3000 (m), 2960 (s), 2925 (s), 2880 (m), 2855 (s), 1470 (m), 1462 (m), 1388 (m), 1360 (m), 1253 (s), 1222 (m), 1200 (m), 1150 (m),1130 (m), 1110 (s), 1098 (m), 1065 (s), 1046 (s), 1023 (s), 1002 (m), 980 (m), 952 (m), 894 (m), 865 (m), 850 (m), 830 (s), 663 (m), 657 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 4.73 (d, *J* = 2.5 Hz, 1 H), 4.09-4.05 (m, 1 H), 3.64 (ddd, *J* = 10.5, 10.5, 1.3 Hz, 1 H), 3.60 (apparent t, *J* = 2.5 Hz, 1 H), 3.62-3.59 (m, 1 H), 3.47 (s, 3 H), 3.47-3.42 (m, 1 H), 1.95-1.85 (m, 2 H), 1.82 (ddd, *J* = 14.3, 9.2, 1.5 Hz, 1 H), 1.60 (dqd, *J* = 10.2, 6.8, 2.5 Hz, 1 H), 1.45 (ddd, *J* = 14.3, 10.7, 2.6 Hz, 1 H), 0.895 (d, *J* = 7.5 Hz, 3 H), 0.887 (apparent s, 18 H), 0.785 (d, *J* = 6.8 Hz, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 100.8, 76.8, 72.2, 69.5, 67.6, 56.8, 41.0, 38.2, 34.9, 25.9, 25.8, 18.1, 14.0, 9.7, -4.2, -4.6, -4.7, -5.0; high resolution mass spectrum (FAB, NBA) *m/z* 485.3080 [(M+Na)$^+$; calcd for $C_{23}H_{50}O_5SiNa$: 485.3094].

α anomer: $[\alpha]^{23}_D$ +54.9° © 1.20, $CHCl_3$); IR ($CHCl_3$) 3670 (w), 3590 (w) 3440 (w, br), 3000 (m), 2960 (s), 2925 (s), 2880 (m), 2855 (s), 1463 (m), 1390 (m), 1360 (m), 1255 (s), 1225 (m), 1192 (m), 1168 (m), 1143 (m), 1102 (s), 1083 (s),1045 (s), 1030 (m), 1002 (m), 963 (m), 932 (m), 862 (m),

833 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 4.25 (d, *J* = 4.2 Hz, 1 H), 3.89 (dddd, *J* = 6.5, 4.6, 4.6, 4.6 Hz, 1 H), 3.80 (ddd, *J* = 9.1, 9.1, 2.3 Hz, 1 H), 3.61 (br dd, *J* = 10.9, 3.4 Hz, 1 H), 3.51 (dd, *J* = 6.5, 4.6 Hz, 1 H), 3.52-3.48 (m, 1 H), 3.33 (s, 3 H), 2.15 (s, br, 1 H), 1.81 (dqd, *J* = 6.9, 6.9, 4.2 Hz, 1 H), 1.72-1.60 (m, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.882 (s, 9 H), 0.879 (s, 9 H), 0.845 (d, *J* = 6.8 Hz, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 104.0, 72.7, 71.3, 70.0, 67.6, 55.7, 38.7, 38.5, 37.3, 25.8, 18.13, 18.08, 15.2, 13.1, -4.4, -4.6, -4.7; high resolution mass spectrum (FAB, NBA) *m/z* 485.3081 [$(M+Na)^+$; calcd for $C_{23}H_{50}O_5Si_2Na$: 485.3094].

EXAMPLE 31

Alcohol 38.

A solution of **37** (276.6 mg, 0.598 mmol) in Et_2O (40 mL) was treated with EtSH (8.90 mL, 120 mmol) and $MgBr_2.Et_2O$ (1.54 g, 5.96 mmol) at room temperature. After 60 h, the mixture was diluted with ethyl acetate (50 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (3% acetone/hexane) provided **38** α (34.4 mg, 12% yield) and **38** β (211.3 mg, 71% yield).

β anomer: colorless oil; $[\alpha]^{23}_D$ +16.6° © 1.18, $CHCl_3$); IR ($CHCl_3$) 3595 (m), 3400 (m, br), 3000 (m), 2960 (s), 2930 (s), 2855 (s), 1655 (w), 1612 (s), 1588 (m), 1510 (s), 1462 (s), 1375 (m), 1360 (m), 1300 (m), 1250 (s, br), 1170 (m), 1080 (s, br), 1030 (s), 1002 (m), 967 (m), 835 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 5.08 (d, *J* = 2.3 Hz, 1 H), 4.04-4.00 (m, 1H), 3.62 (ddd, *J* = 10.4, 10.4, 1.0 Hz, 1 H), 3.60 (ddd, *J* = 11.1, 11.1, 4.2 Hz, 1 H), 3.56 (apparent t, *J* = 2.7 Hz, 1 H), 3.43 (ddd, *J* = 11.7, 7.9, 4.1 Hz, 1 H), 2.70 (dq, *J* = 12.7, 7.4 Hz, 1 H), 2.67 (dq, *J* = 12.8, 7.5 Hz, 1

H), 1.95 (dd, J = 7.9, 4.8 Hz, 1 H), 1.86 (qdd, J = 7.1, 2.7, 2.7 Hz, 1 H), 1.79 (ddd, J = 14.4, 9.0, 1.4 Hz, 1 H), 1.66-1.59 (m, 1 H), 1.57 (s, 3 H), 1.45 (ddd, J = 14.4, 10.5, 2.7 Hz, 1 H), 1.27 (apparent t, J = 7.4 Hz, 1 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.79 (d, J = 6.8 Hz, 3 H), 0.083 (s, 3 H), 0.075 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 81.0, 76.2, 75.0, 69.8, 67.6, 41.9, 38.3, 34.5, 25.9, 25.8, 25.2, 18.1, 15.2, 14.4, 11.5, -4.2, -4.56, -4.63, -4.9; high resolution mass spectrum (FAB, NBA) m/z 515.3037 [(M+Na); calcd for $C_{24}H_{52}O_4SSi_2Na$: 515.3023].

α anomer: colorless oil; $[\alpha]^{23}_D$ +94.5° © 0.33, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3580 (w), 3440 (w, br), 3010 (m), 2960 (s), 2930 (s), 2880 (m), 2860 (s), 1513 (w), 1470 (m), 1462 (m), 1390 (m), 1380 (m), 1360 (m), 1257 (s), 1225 (m), 1200 (m), 1114 (m), 1070 (s), 1047 (s), 1022 (m), 1002 (m), 957 (m), 860 (m), 833 (s), 705 (s), 660 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 4.76 (d, J = 3.1 Hz, 1 H), 4.04 (ddd, J = 9.8, 9.8, 1.8 Hz, 1 H), 3.84 (dddd, J = 5.0, 5.0, 5.0, 5.0 Hz, 1 H), 3.57 (dd, J = 11.0, 4.2 Hz, 1 H), 3.53 (apparent t, J = 4.0 Hz, 1 H), 3.47 (dd, J = 11.0, 4.7 Hz, 1 H), 2.57 (dq, J = 12.8, 7.5 Hz, 1 H), 2.54 (dq, J = 12.8, 7.5 Hz, 1 H), 1.97-1.91 (m, 1 H), 1.75 (ddd, J = 14.7, 6.1 Hz, 2.0, 1 H), 1.72-1.65 (m, 1 H), 1.60 (ddd, J = 14.9, 10.0, 5.1 Hz, 1 H), 1.60-1.50 (br, 1 H), 1.23 (apparent t, J = 7.4 Hz, 3 H), 1.06 (d, J = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.12 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 85.3, 73.8, 71.5, 69.2, 67.5, 40.6, 38.2, 36.4, 26.4, 26.1, 25.9, 18.2, 18.1, 17.5, 14.7, 13.9, -4.2, -4.4, -4.8; high resolution mass spectrum (FAB, NBA) m/z 515.3045 [$(M+Na)^+$; calcd for $C_{24}H_{52}O_4SSi_2Na$: 515.3023].

EXAMPLE 32

Fragment (+)-C.

A solution of DMSO (100 μL, 1.42 mmol) in CH_2Cl_2 (2.0 mL) was cooled to -78 °C and oxalyl chloride (55.0 μl, 0.630 mmol) was introduced dropwise. After 15 min. a cooled (-78 °C) solution of **38** α (104.8 mg, 0.213 mmol) in CH_2Cl_2 (1.0 mL) was introduced via cannula (2 x 500 μL rinse). The resultant milky solution was stirred for 15 min at -78 °C and *I*-Pr_2NEt (370 μl, 2.12 mmol) was added dropwise. The reaction mixture was stirred for 0.5 h, slowly warmed to room temperature (15 min), and quenched with aqueous $NaHSO_4$ (1.0 M, 4.0 mL). The organic phase was diluted with ether (30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (2% ethyl acetate/hexane) furnished (+)-**C** (88.8 mg, 86% yield) as a colorless oil: $[\alpha]^{23}_D$ +11.2° © 1.42, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2935 (s), 2880 (s), 2860 (s), 1735 (s), 1470 (m), 1460 (m), 1380 (m), 1360 (m), 1320 (m), 1295 (w), 1265 (s), 1153 (m), 1120 (m), 1080 (m), 1060 (s), 1043 (s), 1025 (s), 1003 (s), 970 (m), 950 (m), 935 (m), 903 (m), 865 (m), 835 (s), 800 (m), 690 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 9.56 (d, *J* = 0.9 Hz, 1 H), 5.07 (d, *J* = 2.3 Hz, 1 H), 4.35 (ddd, *J* = 7.9, 2.2, 0.6 Hz, 1 H), 3.70 (ddd, *J* = 10.3, 10.3, 1.5 Hz, 1 H), 3.57 (apparent t, *J* = 2.7 Hz, 1 H), 2.71-2.60 (m, 2 H), 1.86 (apparent qt, *J* = 7.1, 2.7 Hz, 1 H), 1.78 (ddd, *J* = 14.1, 10.4, 7.8 Hz, 1 H), 1.72-1.66 (m, 1 H), 1.67 (ddd, *J* = 10.3, 3.9, 1.8 Hz, 1 H), 1.25 (apparent t, *J* = 7.4 Hz, 3 H), 1.00 (d, *J* = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.78 (d, *J* = 6.8 Hz, 3 H), 0.10 (s, 3 H), 0.04 (s, 6 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 202.6, 81.2, 76.1, 74.9, 73.7, 41.9, 35.8, 34.4, 25.82, 25.79, 25.2, 18.2, 18.1, 15.3, 14.3, 11.5, -4.2, -4.5, -4.9, -5.2; high resolution mass spectrum (CI, NH_3) *m/z* 491.3058 [$(M+H)^+$; calcd for $C_{24}H_{51}O_4SSi_2$: 491.3046].

EXAMPLE 33

Fragment (-)-B.

From vinyl bromide (-)-**22**: A solution of (-)-**22** (3.78 g, 8.04 mmol) in HMPA/DMF (2:1, 6 mL) was added to a mixture of KI (4.15 g, 250 mmol), $NiBr_2$ (34.9 mg, 0.160 mmol), and Zn powder (23.2 mg, 0.355 mmol). The mixture was stirred at room temperature for 15 min then heated to 90 °C. The green color mixture turned black-brown after 5 min and dark green after 1 h. After additional 1 h at 90 °C, the mixture was cooled to room temperature, diluted with ethyl acetate (200 mL), washed with brine (4 x 200 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (2% ethyl acetate/hexane) provided **B** (3.59 g, containing 13% unreacted vinyl bromide) as a colorless oil.

From aldehyde (+)-**18**: A suspension of $EtPh_3P^+I^-$ (15.1 g, 36.1 mmol) in THF (200 mL) was treated with *n*-BuLi (1.6 M in hexane, 23.0 mL, 36.8 mmol) at room temperature over 10 min. After an additional 10 min, the resultant red solution was added via cannula to a cooled (-78°C) solution of I_2 (8.02 g, 31.6 mmol) in THF (300 mL) over 15 min. The yellow slurry formed was stirred at -78 °C for 5 min and at -23 °C for 10 min. NaHMDS (1.0 M in THF, 31.0 mL, 31.0 mmol) was added over 8 min and the mixture stirred 15 min further. A solution of aldehyde (+)-**18** (6.96 g, 18.3 mmol) in THF (50 mL) was introduced via cannula (10mL rinse), and the reaction mixture was stirred at -23 °C for 10 min, warmed to room temperature, stirred for 3 h, and then quenched with MeOH (10 mL). Following concentration and filtration through a silica column (50% ethyl acetate/hexane), the filtrate was washed with saturated aqueous $Na_2S_2O_3$, brine (300 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% ethyl acetate/hexane) furnished **B** (6:1 Z/E, 3.94 g, 41% yield) as a colorless oil.

An analytical sample of (-)-**B** was obtained by reversed-phase HPLC (gradient elution, 90% CH_3CN/H_2O -> 100% CH_3CN): $[\alpha]^{23}_D$ -23° © 0.30, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2960 (s), 2930 (s), 2880 (m), 2855 (s), 1610 (m), 1588 (w), 1510 (s), 1463 (m), 1453 (m), 1428 (m), 1405 (w), 1390 (m), 1377 (m), 1360 (m), 1303 (m), 1250 (s), 1180 (m), 1172 (m), 1080 (s, br), 1033 (s), 1002 (m), 948 (m), 935 (m), 922 (m), 833 (s), 803 (m), 760 (m, br), 720 (m), 658 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.25 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.28 (apparent dd, J = 8.9, 1.4 Hz, 1 H), 4.41 (ABq, J_{AB} = 7.0 Hz, $\Delta\delta_{AB}$ = 10.2 Hz, 2 H), 3.80 (s, 3 H), 3.60 (apparent t, J = 5.3 Hz, 1 H), 3.51 (dd, J = 9.1, 5.1 Hz, 1 H), 3.23 (dd, J = 9.0, 8.0 Hz, 1 H), 2.54-2.47 (m, 1 H), 2.44 (d, J = 1.4 Hz, 3 H), 2.00-1.92 (m, 1 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.1, 139.6, 131.0, 129.1, 113.7, 98.9, 76.5, 72.6, 72.5, 55.3, 44.5, 38.7, 33.5, 26.1, 18.4, 14.7, 14.5, -3.95, -3.99; high resolution mass spectrum (FAB, NBA) m/z 541.1626 [$(M+Na)^+$; calcd for $C_{23}H_{39}O_3ISiNa$: 541.1611].

EXAMPLE 34

Olefin (-)-39.

$ZnCl_2$ (1.32 g, 9.69 mmol) was dried at 160 °C under vacuum overnight and then treated with a solution of (-)- **A** (5.25 g, 9.59 mmol) in dry Et_2O (50 mL) via a cannula (2 x 25 mL rinse). The mixture was stirred at room temperature until most of the $ZnCl_2$ dissolved and cooled to -78 °C. *t*-BuLi (1.7 M in pentane, 17.0 mL) was added over 30 min, and the resultant solution was stirred 15 min further, warmed to room temperature, and stirred for 1 h. The solution was added by cannula to a mixture of **B** (3.21 g, 6.19 mmol; 6:1 Z/E) and $Pd(PPh_3)_4$ (364.0 mg, 0.315 mmol). The mixture was covered with aluminum foil, stirred overnight,

and then diluted with ethyl acetate (100 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% ethyl acetate/hexane) gave (-)-**39** (3.32 g, 66% yield) as a white semisolid: $[\alpha]^{23}_{D}$ -28.6° © 1.53, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2970 (s), 2940 (s), 2865 (s), 1620 (m), 1590 (w), 1520 (s), 1465 (s), 1445 (m), 1390 (m), 1380 (m), 1360 (m), 1305 (m), 1250 (s), 1175 (m), 1115 (s), 1080 (s), 1040 (s), 970 (m), 940 (w), 860 (m), 835 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.36 (d, J = 8.7 Hz, 2 H), 7.22 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 6.84 (d, J = 8.9 Hz, 2 H), 5.37 (s, 1 H), 5.00 (d, J = 10.2 Hz, 1 H), 4.36 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 17.4 Hz, 2 H), 4.08 (dd, J = 11.2, 4.7 Hz, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.61 (dd, J = 7.1, 1.8 Hz, 1 H), 3.51 (dd, J = 9.9, 1.7 Hz, 1 H), 3.47 (apparent t, J = 11.0 Hz, 1 H), 3.46 (dd, J = 9.1, 5.0 Hz, 1 H), 3.38 (dd, J = 6.0, 4.8 Hz, 1 H), 3.19 (apparent t, J = 8.8 Hz, 1 H), 2.51 (ddq, J = 10.1, 6.5, 6.5 Hz, 1 H), 2.32 (apparent t, J = 12.2 Hz, 1 H), 2.08-2.02 (m, 1 H), 1.99-1.93 (m, 2 H), 1.88 (dqd, J = 7.1, 7.1, 1.8 Hz, 1 H), 1.67 (br d, J = 11.1 Hz, 1 H), 1.55 (d, J = 0.5 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.74 (d, J = 6.3 Hz, 3 H), 0.73 (d, J = 6.4 Hz, 3 H), 0.03 (s, 3 H), 0.013 (s, 3 H), 0.008 (s, 3 H), 0.003 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 159.0, 132.0, 131.5, 131.2, 131.1, 129.0, 127.3, 113.7, 113.5, 101.1, 83.4, 78.49, 78.46, 73.3, 72.6, 72.5, 55.3, 38.8, 38.2, 37.5, 35.6, 33.7, 30.8, 26.27, 26.25, 23.1, 18.42, 18.40, 17.0, 14.6, 12.6, 12.1, 10.9, -3.5, -3.7, -3.8, -3.9; high resolution mass spectrum (FAB, NBA) m/z 835.5315 [$(M+Na)^+$; calcd for $C_{47}H_{80}O_7Si_2Na$: 835.5341].

Anal. Calcd for $C_{47}H_{80}O_7Si_2$: C, 69.41; H, 9.91. Found: C, 69.52; H, 10.10.

EXAMPLE 35

Alcohol (-)-40.

A solution of olefin (-)-**39** (2.65 g, 3.26 mmol) in CH_2Cl_2 (32 mL) was cooled to 0 °C and treated with H_2O (1.50 mL) and DDQ (774 mg, 3.41 mmol). After 4 h, the mixture was diluted with CH_2Cl_2 (20 mL), dried over $MgSO_4$, and filtered through a silica column (50% ethyl acetate/hexane). Following concentration, the residue was dissolved in EtOH (50 mL) and treated with $NaBH_4$ (500 mg, excess) at room temperature to reduce the contaminated *p*-methoxybenzyl aldehyde. After 0.5 h, the mixture was quenched with saturated aqueous NH_4Cl (50 mL) at 0 °C then concentrated. The residue was partitioned between CH_2Cl_2 (200 mL) and water (100 mL). The organic phase was washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexane) provided (-)-**40** (2.06 g, 91% yield) as a white solid. mp 99-100 °C; $[\alpha]^{23}_D$ -25.4° © 1.35, $CHCl_3$); IR ($CHCl_3$) 3520 (w), 3010 (m), 2960 (s), 2940 (s), 2880 (m), 2860 (m), 1620 (m), 1593 (w), 1520 (m), 1565 (m), 1390 (m), 1360 (m), 1255 (s), 1175 (m), 1165 (m), 1117 (m), 1075 (s), 1037 (s), 1025 (s), 1005 (m), 982 (m), 965 (m), 930 (w), 835 (s), 800 (m), 705 (w), 675 (w), 660 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.36 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 5.37 (s, 1 H), 5.01 (d, J = 10.1 Hz, 1 H), 4.09 (dd, J = 11.2, 4.7 Hz, 1 H), 3.79 (s, 3 H), 3.65 (dd, J = 10.4, 4.7 Hz, 1 H), 3.63 (dd, J = 7.0, 1.8 Hz, 1 H), 3.54-3.50 (m, 1 H), 3.51 (dd, J = 10.0, 2.0 Hz, 1 H), 3.47 (apparent t, J = 11.2 Hz, 1 H), 3.41 (dd, J = 6.6, 4.0 Hz, 1 H), 2.59 (ddq, J = 13.2, 6.7, 6.7 Hz, 1 H), 2.33 (apparent t, J = 12.2 Hz, 1 H), 2.24 (apparent t, J = 5.5 Hz, 1 H), 2.09-1.95 (m, 2 H), 1.89 (dqd, J = 7.0, 7.0, 1.7 Hz, 1 H), 1.84-1.77 (m, 1 H), 1.72 (br d J = 11.0 Hz, 1 H), 1.58 (d, J = 0.8 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.910 (s, 9

H), 0.905 (s, 9 H), 0.75 (d, J = 7.1 Hz, 3 H), 0.74 (d, J = 7.1 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 133.0, 131.5, 130.5, 127.3, 113.4, 101.0, 83.3, 81.6, 78.4, 73.3, 65.4, 55.3, 38.5, 38.2, 37.6, 37.0, 33.7, 30.8, 26.17, 26.16, 23.2, 18.4, 18.3, 17.4, 15.7, 12.6, 12.1, 10.9, -3.57, -3.61, -3.66, -3.9; high resolution mass spectrum (CI, NH_3) m/z 693.4918 [$(M+H)^+$; calcd for $C_{39}H_{73}O_6Si_2$: 693.4945].

Anal. Calcd for $C_{39}H_{72}O_6Si_2$: C, 67.58; H, 10.47. Found: C, 67.30; H, 10.54.

EXAMPLE 36

Phosphonium Salt (-)-49.

A solution of alcohol (-)-**40** (402.8 mg, 0.577 mmol) in PhH/Et_2O (1:2, 45 mL) was treated with PPh_3 (532 mg, 2.03 mmol) and imidazole (158 mg, 2.32 mmol). After the imidazole dissolved, I_2 (437 mg, 1.72 mmol) was added under vigorous stirring. The mixture was stirred 2 h and then treated with NEt_3 (2 mL). The resultant yellow suspension was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $Na_2S_2O_3$ (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (2 x 100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Filtration through a short silica column (NEt_3/ethyl acetate/hexane, 2:10:90) removed triphenylphosphine oxide, affording the impure iodide **42**. Preparative TLC (500 mm silica gel plate, 4% acetone/hexane) furnished an analytical sample as an unstable white solid: ^1H NMR (500 MHZ, $CDCl_3$) d 7.35 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 5.37 (s, 1 H), 5.02 (d, J = 10.2 Hz, 1 H), 4.08 (dd, J = 11.2, 4.7 Hz, 1 H), 3.78 (s, 3 H), 3.62 (dd, J = 7.0, 1.8 Hz, 1 H), 3.51 (dd, J = 9.9, 1.7 Hz, 1 H), 3.47 (apparent t, J = 11.1 Hz, 1 H), 3.37 (dd, J = 6.3, 4.3 Hz, 1 H), 3.32 (dd, J = 9.6, 4.5 Hz, 1 H), 2.99 (dd, J = 9.5, 8.6 Hz, 1 H), 2.50 (ddq, J = 10.2, 6.5, 6.5 Hz, 1 H), 2.31

(apparent t, J = 12.2 Hz, 1 H), 2.08-1.95 (m, 2 H), 1.88 (dqd, J = 7.1, 7.1, 1.7 Hz, 1 H), 1.85-1.78 (m, 1 H), 1.74 (br d, J = 11.7 Hz, 1 H), 1.57 (apparent s, 3 H), 1.01 (apparent d, J = 7.0 Hz, 6 H), 0.91-0.89 (m, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.74 (d, J = 6.8 Hz, 3 H), 0.73 (d, J = 6.7 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$/1% pyridine-d_5, 20 mg sample) d 159.8, 132.9, 131.5, 130.4, 127.3, 113.5, 101.1, 83.3, 79.6, 78.5, 73.3, 55.3, 41.4, 38.3, 37.6, 36.0, 33.7, 30.8, 26.20, 26.17, 23.2, 18.4, 17.7, 17.3, 13.5, 12.6, 12.2, 10.9, -3.5, -3.6, -4.0; high resolution mass spectrum (FAB, NBA) m/z 803.3935 [$(M+H)^+$; calcd for $C_{39}H_{72}O_5ISi_2$: 803.3963]. The very sensitive impure iodide (obtained by filtration through silica) was quickly mixed with I-Pr_2NEt (300 μL, 1.72 mmol) and PPh_3 (2.47 g, 9.42 mmol). The mixture was heated at 80 °C for 24 h, then cooled to room temperature and extracted with hexane (2 x 30 mL). The residue was purified by flash chromatography (2% MeOH/$CHCl_3$) furnishing (-)-**49** (224.9 mg, 37% yield from (-)-**39**) as a pale yellow foam. The hexane extract was concentrated and purified by flash chromatography (2% ethyl acetate/hexane) affording a mixture of cyclization products (200 mg). Further purification by normal phase HPLC (1.5% ethyl acetate/hexane) provided (-)-**50** as the major cyclization product.

Wittig reagent (-)-**49**: $[\alpha]^{23}_D$ -25.3° © 1.48, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2930 (s), 2860 (m), 1615 (m), 1590 (w), 1515 (m), 1485 (w), 1460 (m), 1440 (m), 1385 (m), 1360 (m), 1300 (m), 1250 (s), 1215 (m, br), 1180 (m), 1110 (s), 1080 (m), 1025 (m), 1005 (m), 965 (m), 945 (w), 860 (m), 830 (s), 732 (m), 725 (m), 710 (m), 680 (m), 653 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$; concentration dependent) d 7.82-7.76 (m, 15 H), 7.35 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 5.35 (s, 1 H), 5.30 (d, J = 10.5 Hz, 1 H), 4.07 (dd, J = 11.2, 4.7 Hz, 1 H), 3.77 (s, 3 H), 3.73-3.67 (m, 2 H), 3.56 (dd, J

= 7.0, 1.8 Hz, 1 H), 3.48 (dd, *J* = 9.8, 1.7 Hz, 1 H), 3.46 (apparent t, *J* = 11.1 Hz, 1 H), 3.31 (ddd, *J* = 15.6, 11.2, 11.2 Hz, 1 H), 2.49 (ddq, *J* = 10.5, 6.4, 6.4 Hz, 1 H), 2.25 (apparent t, *J* = 12.1 Hz, 1 H), 2.10-1.92 (m, 3 H), 1.85 (dqd, *J* = 7.1, 7.1, 1.8 Hz, 1 H), 1.57-1.52 (m, 1 H), 1.56 (s, 3 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.852 (s, 9 H), 0.849 (s, 9 H), 0.72-0.71 (m, 3 H), 0.71 (d, *J* = 6.6 Hz, 3 H), 0.69 (d, *J* = 6.9 Hz, 3 H), 0.10 (s, 3 H), -0.02 (s, 3 H), -0.03 (s, 3 H), -0.07 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 135.2 (J_{CP} = 2.6 Hz), 133.5 (J_{CP} = 10.0 Hz), 132.9, 131.4, 130.6 (J_{CP} = 12.6 Hz), 130.3, 127.3, 118.4 (J_{CP} = 85.5 Hz), 113.4, 101.0, 83.2, 80.1 (J_{CP} = 14.0 Hz), 78.3, 73.2, 55.3, 38.1, 37.4, 36.0, 33.7 (J_{CP} = 4.4 Hz), 33.6, 30.7, 26.1, 25.5 (J_{CP} = 49.7 Hz), 22.9, 18.33, 18.29, 17.2, 17.1, 12.5, 12.1, 10.9, -3.2, -3.6, -3.7, -4.0; high resolution mass spectrum (FAB, NBA) *m/z* 937.5708 [$(M-I)^+$; calcd for $C_{57}H_{86}O_5PSi_2$: 937.5751].

Olefin (-)50: white solid; mp 80-82 °C; $[\alpha]^{23}_D$ -18° © 0.48, $CHCl_3$); IR ($CHCl_3$) 2955 (s), 2920 (s), 2880 (m), 2850 (s), 1640 (w), 1613 (m), 1588 (w), 1517 (m), 1460 (m), 1387 (m), 1360 (m),1300 (m), 1250 (s), 1178 (m), 1170 (m), 1160 (m), 1115 (m), 1080 (m), 1023 (s), 1000 (m), 980 (m), 960 (m), 930 (w), 887 (m), 855 (m), 830 (m), 715 (m) cm^{-1}; ^{1}H NMR (500 MHZ, C_6D_6) d 7.62 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 5.46 (s, 1 H), 5.00 (s, 1 H), 4.95 (s, 1 H), 3.93 (dd, *J* = 11.1, 4.7 Hz, 1 H), 3.89 (dd, *J* = 7.2, 1.5 Hz, 1 H), 3.55 (dd, *J* = 9.9, 1.9 Hz, 1 H), 3.51 (apparent t, *J* = 5.9 Hz, 1 H), 3.27 (s, 3 H), 3.22 (apparent t, *J* = 11.0 Hz, 1 H), 2.32 (dd, *J* = 13.6, 3.5 Hz, 1 H), 2.27-2.20 (m, 1 H), 2.16 (dd, *J* = 13.7, 9.5 Hz, 1 H), 2.07-1.92 (m, 4 H), 1.87-1.80 (m, 1 H), 1.50-1.42 (m, 1 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 1.04 (s, 9 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 1.00 (s, 9 H),

0.41 (d, J = 6.7 Hz, 3 H), 0.13 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8 (q), 150.7 (q), 131.5 (q), 127.3, 113.4, 108.3 (CH_2), 101.0, 83.2, 81.9, 78.1, 73.3 (CH_2), 55.2, 49.9, 44.9, 41.4 (CH_2), 39.0 (CH_2), 38.3, 36.6, 33.4, 30.8, 26.3, 25.9, 18.5 (q), 18.2 (q), 17.8, 15.5, 12.9, 12.1, 11.0, -3.4, -3.7, -4.6, -4.7; high resolution mass spectrum (FAB, NBA) m/z 697.4642 [$(M+Na)^+$; calcd for $C_{39}H_{70}O_5Si_2Na$: 697.4659].

EXAMPLE 37

Model Olefin (+)-43.

NaHMDS (0.6 M in PhMe, 9.46 mL, 5.68 mmol) was added over 10 min to a suspension of $(CH_3)_2CHP^+Ph_3\ I^-$ (2.52 g, 5.83 mmol) in PhMe (20 mL) at room temperature. After 15 min, the mixture was cooled to -78 °C, and aldehyde (+)-**18** (1.46 g, 3.84 mmol) in PhMe (15 mL) was introduced via a cannula (15mL rinse). After 20 min at -78 °C and 30 min at room temperature, the reaction was quenched with MeOH (1.0 mL). The solution was separated, and the oil residue was extracted with hexane (3 x 30 mL). The combined organic solutions were then concentrated and, and flash chromatography (2% ethyl acetate/hexane) provided (+)-**43** (1.44 g, 92% yield) as a colorless oil: $[\alpha]^{23}_D$ +8.07° © 2.57, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2925 (s), 2880 (s), 2855 (s), 1610 (m), 1585 (m), 1510 (s), 1460 (s), 1375 (m), 1360 (m), 1300 (m), 1245 (s), 1172 (m), 1085 (s, br), 1035 (s), 1003 (m), 970 (m), 950 (m), 935 (m), 862 (s), 835 (s) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.23 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 4.92 (d-quintet, J = 9.7, 1.4 Hz, 1 H), 4.37 (apparent s, 2 H), 3.78 (s, 3 H), 3.49 (dd, J = 9.2, 4.9 Hz, 1 H), 3.39 (dd, J = 6.3, 4.5 Hz, 1 H), 3.19 (dd, J = 9.0, 8.4 Hz, 1 H), 2.49 (ddq, J = 9.6, 6.7, 6.7 Hz, 1 H), 2.00-1.92 (m, 1 H), 1.63 (d, J = 1.2 Hz, 3 H), 1.55 (d, J = 1.3 Hz, 3 H), 0.945 (d, J = 7.0 Hz, 3 H), 0.874 (d, J = 6.7

Hz, 3 H), 0.873 (s, 9 H), 0.01 (apparent s, 6 H); ^{13}C NMR (125 MHZ, $CDCl_3$) 159.0, 131.1, 129.7, 129.4, 129.1, 113.7, 78.6, 72.6, 55.3, 38.5, 36.0, 26.2, 25.8, 18.4, 17.9, 17.0, 14.8, -3.88, -3.95; high resolution mass spectrum (CI, NH_3) *m/z* 407.2984 [$(M+H)^+$; calcd for $C_{24}H_{43}O_3Si$: 407.2981].

EXAMPLE 38

Alcohol (+)-44.

A mixture of olefin (+)-**43** (387.6 mg, 0.954 mmol) in CH_2Cl_2 (10 mL) was treated with H_2O (500 μL) and DDQ (320 mg, 1.41 mmol). After 30 min at room temperature, the mixture was filtered through a short silica plug (50% ethyl acetate/hexane) and concentrated. Flash chromatography (3% ethyl acetate/hexane) provided (+)-**43** (273.1 mg, 99% yield) as a colorless oil: $[\alpha]^{23}_D$ +17.5° © 2.80, $CHCl_3$); IR ($CHCl_3$) 3620 (w), 3500 (m, br), 2955 (s), 2925 (s), 2880 (s), 2860 (s), 1460 (s), 1405 (m), 1375 (m), 1360 (m), 1337 (m), 1252 (s), 1070 (s), 1050 (s), 1015 (s), 1002 (s), 978 (m), 933 (m), 832 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 4.92 (apparent d quintet, *J* = 9.7, 1.4 Hz, 1 H), 3.66 (ddd, *J* = 11.0, 4.4, 4.4 Hz, 1 H), 3.52 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1 H), 3.42 (dd, *J* = 6.8, 4.0 Hz, 1 H), 2.57 (ddq, *J* = 9.6, 6.8, 6.8 Hz, 1 H), 2.45 (apparent t, *J* = 5.2 Hz, 1 H), 1.85-1.78 (m, 1 H), 1.65 (d, *J* = 1.3 Hz, 3 H), 1.59 (d, *J* = 1.3 Hz, 3 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 130.7, 128.5, 81.7, 65.5, 38.1, 37.4, 26.2, 25.8, 18.3, 17.9, 17.4, 15.9, -3.7, -3.9; high resolution mass spectrum (CI, NH_3) *m/z* 287.2418 [$(M+H)^+$; calcd for $C_{16}H_{35}O_2Si$: 287.2406].

EXAMPLE 39

Wittig reagent (+)-46.

Iodine (1.08 g, 4.24 mmol) was added to a solution

of alcohol (+)-**44** (810 mg, 2.83 mmol), PPh_3 (1.11 g, 4.24 mmol) and imidazole (289 mg, 4.24 mmol) in benzene/ether (1:2, 21 mL) under vigorous stirring at room temperature. After 40 min, the mixture was diluted with ether (100 mL), washed with saturated $Na_2S_2O_3$ (50 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane) provided a mixture of **45/47/48** (1.06 g, 97% yield, 18:1:1) as a colorless oil; This material was then treated with *I*-Pr_2NEt (928 μL, 5.33 mmol) and PPh_3 (7.01 g, 26.7 mmol) then heated at 80 °C for 13 h. The mixture was extracted with hexane (3 x 100 mL). The residue was purified by flash chromatography (2% MeOH/$CHCl_3$) providing Wittig reagent (+)-**48** (207.1 mg, 38% yield from (+)-**46**) as a pale yellow foam. The hexane extract was concentrated and purified by flash chromatography (hexane) affording a mixture of two cyclization products (380 mg) and further purification by preparative TLC (hexane) afforded (-)-**49** and (-)-**50**.

Wittig reagent (+)-**46**: $[\alpha]^{23}_D$ +4.8° © 1.23, $CHCl_3$); IR ($CHCl_3$) 2940 (s), 2860 (m), 1588 (w), 1482 (w), 1468 (m), 1460 (m), 1440 (s), 1380 (m), 1360 (w), 1310 (w), 1253 (m), 1230 (m), 1210 (m), 1110 (s), 1080 (m), 1050 (m), 1018 (m), 1000 (m), 995 (m), 860 (m), 832 (s), 800 (m), 708 (m), 680 (m), 652 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$; concentration dependent) d 7.81-7.67 (m, 15 H), 4.92 (d, J = 9.7 Hz, 1 H), 3.50 (apparent t, J = 5.3 Hz, 1 H), 3.38 (ddd, J = 14.9, 14.9, 1.5 Hz, 1 H), 3.25 (ddd, J = 15.6, 11.1, 11.1 Hz, 1 H), 2.42 (ddq, J = 9.7, 6.6, 6.6 Hz, 1 H), 2.10-2.00 (m, 1 H), 1.53 (s, 3 H), 1.43 (s, 3 H), 0.83 (s, 9 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.75 (d, J = 6.8 Hz, 3 H), 0.03 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d, 135.3 (J_{cp} = 2.8 Hz), 133.3 (J_{cp} = 9.9 Hz), 131.0, 130.6 (J_{cp} = 12.4 Hz), 128.0, 118.2 (J_{cp} = 85.6 Hz), 80.4 (J_{cp} = 13.3 Hz), 36.0, 33.0 (J_{cp} = 4.0 Hz), 26.1, 25.6, 25.1 (J_{cp} = 50.8 Hz), 18.3, 18.1,

17.9, 16.4, -3.3, -4.0; high resolution mass spectrum (FAB, NBA) *m/z* 531.3221 [(M-I)$^+$; calcd for $C_{34}H_{48}OPSi$: 531.3213].

Olefin (-)-47: Colorless oil; $[\alpha]^{23}_D$ -14° © 0.36, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2930 (s), 2860 (s), 1470 (m), 1460, 1370 (m), 1360 (m), 1250 (m), 1206 (w), 1165 (m), 1140 (m), 1070 (s), 1020 (s), 1000 (m), 932 (w), 908 (w), 897 (w), 853 (m), 830 (s) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 3.63 (d, br, *J* = 3.6 Hz, 1 H), 2.50 (apparent q, *J* = 7.3 Hz, 1 H), 2.28 (ddd, *J* = 15.5, 7.7, 0.8 Hz, 1 H), 2.13-2.03 (m, 1 H), 1.99-1.91 (m, 1 H), 1.60 (apparent br s, 3 H), 1.57 (apparent d, *J* = 0.8 Hz, 1 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 0.91 (d, *J* = 7.4 Hz, 3 H), 0.85 (s, 9 H), 0.01 (apparent s, 6 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 138.9 (q), 122.0 (q), 82.9, 46.1, 36.4, 35.8 (CH_2), 25.9, 21.2, 20.4, 18.3 (q), 18.0, 14.3, -4.6, -4.8; high resolution mass spectrum (CI, NH_3) *m/z* 269.2310 [(M+H)$^+$; calcd for $C_{16}H_{33}OSi$: 269.2300].

Olefin (-)-48: Colorless oil; $[\alpha]^{23}_D$ -3.8° © 0.24, $CHCl_3$); IR ($CHCl_3$) 2953 (s), 2925 (s), 2880 (m), 2855 (m), 1638 (w), 1470 (m), 1460 (m), 1385 (w), 1373 (m), 1360 (w), 1250 (m), 1135 (m), 1117 (m), 1100 (m), 1075 (m), 1028 (m), 1000 (m), 932 (w), 865 (m), 830 (s) cm^{-1}; ^{1}H NMR (500 MHZ, C_6D_6) d 4.84-4.83 (m, 1 H), 4.79-4.77 (m, 1 H), 3.46 (apparent t, *J* = 5.3 Hz, 1 H), 1.94-1.88 (m, 1 H), 1.87-1.78 (m, 2 H), 1.73 (ddd, *J* = 12.4, 7.3, 7.3 Hz, 1 H), 1.66 (apparent dd, *J* = 1.3, 0.8 Hz, 3 H), 1.45 (ddd, *J* = 12.2, 10.3, 8.7 Hz, 1 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.99 (s, 9 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHZ, C_6D_6) d 147.4 (q), 110.3 (CH_2), 82.3, 53.1, 45.4, 37.5 (CH_2), 37.3, 26.1, 19.3, 18.4 (q), 18.0, 15.6, -4.4, -4.5; high resolution mass spectrum (CI, NH_3) *m/z* 269.2315 [(M+H)$^+$; calcd for $C_{16}H_{33}OSi$: 269.2300].

EXAMPLE 40

Alcohol (+)-51.

A solution of olefin (+)-**44** (70.9 mg, 0.28 mmol) in EtOH/EtOAc (1:8, 4.5 mL) was treated with Pd/C (10% wet, E101 NE/W, 15.2 mg) under H_2 atmosphere for 18 h. The mixture was then filtered through a short silica pipet and concentrated. Flash chromatography (5% ethyl acetate/hexane) provided (+)-**51** (70.8 mg, 100% yield) as a colorless oil. $[\alpha]^{23}_{D}$ +28° © 0.15, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3620 (w), 3500 (w, br), 3010 (m), 2960 (s), 2935 (s), 2900 (m), 2885 (m), 2860 (m), 1522 (w), 1510 (w), 1470 (m), 1426 (m), 1420 (m), 1412 (m), 1387 (m), 1370 (m), 1255 (m), 1205 (m), 1070 (m), 1030 (m), 1013 (m), 1002 (m), 980 (m), 925 (m), 833 (s), 720 (m), 665 (m), 658 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 3.60-3.56 (m, 2 H), 3.46 (dd, J = 5.5, 3.8 Hz, 1 H), 2.46 (br s, 1 H), 1.89-1.81 (m, 1 H), 1.74-1.66 (m, 1 H), 1.64-1.56 (m, 1 H), 1.21 (ddd, J = 13.3, 8.9, 4.6 Hz, 1 H), 1.09 (ddd, J = 13.7, 9.6, 5.3 Hz, 1 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.9 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.095 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 81.3, 66.3, 42.5, 37.8, 35.7, 26.1, 25.4, 23.8, 21.8, 16.4, 15.1, -3.9, -4.1; high resolution mass spectrum (CI, NH_3) *m/z* 289.2565 [$(M+H)^+$; calcd for $C_{16}H_{37}O_2Si$: 289.2562].

EXAMPLE 41

Iodide (+)-52.

A solution of alcohol (+)-**51** (150 mg, 0.520 mmol), PPh_3 (205 mg, 0.780 mmol) and imidazole (53 mg, 0.780 mmol) in benzene/ether (1:2; 6.0 mL) was treated with iodine (198 mg, 0.780 mmol) under vigorous stirring at room temperature. After 40 min, the mixture was diluted with ether (100 mL), washed with saturated $Na_2S_2O_3$ (50 mL), brine (100 mL), dried

over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane) provided (+)-**51** (195 mg, 94% yield) as a colorless oil: $[\alpha]^{23}_{D}$ +24.2° © 2.21, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2935 (s), 2900 (m), 2860 (s), 1470 (m), 1463 (m), 1425 (w), 1405 (w), 1382 (m), 1368 (m), 1360 (m), 1290 (w), 1255 (s), 1190 (m), 1170 (m), 1082 (s), 1065 (m), 1028 (m), 1003 (m), 970 (w), 932 (w), 832 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 3.41 (dd, J = 9.6, 3.7 Hz, 1 H), 3.38 (dd, J = 6.3, 2.6 Hz, 1 H), 3.10 (dd, J = 9.6, 7.5 Hz, 1 H), 1.72-1.56 (m, 3 H), 1.17 (ddd, J = 13.4, 8.3, 5.4 Hz, 1 H), 1.09 (ddd, J = 13.3, 5.9, 2.1 Hz, 1 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 79.1, 43.7, 39.8, 33.8, 26.2, 25.3, 23.5, 22.0, 18.7, 18.5, 15.9, 14.4, -3.65, -3.71; high resolution mass spectrum (CI, NH_3) m/z 399.1572 [$(M+H)^+$; calcd for $C_{16}H_{36}OISi$: 399.1580].

EXAMPLE 42

Wittig Reagent (+)-53.

A mixture of Iodide (+)-**52** (195 mg, 0.489 mmol) and benzene (100 mL) was treated with I-Pr_2NEt (85 μL, 0.488 mmol) and PPh_3 (1.28 g, 4.88 mmol), then heated at 70 °C for 24 h. The mixture was extracted with hexane (3 x 20 mL). The residue was purified by flash chromatography (3% $MeOH/CHCl_3$) furnishing (+)-**53** (303 mg, 94% yield) as a white foam; $[\alpha]^{23}_{D}$ +3.3° © 2.14, $CHCl_3$); IR ($CHCl_3$) 2950 (s), 2930 (s), 2855 (m), 1588 (w), 1482 (w), 1463 (m), 1438 (s), 1385 (m), 1365 (w), 1253 (m), 1225 (m), 1207 (m), 1110 (s), 1080 (m), 1032 (m), 1000 (m), 832 (s), 804 (m), 708 (m), 680 (m), 653 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.83-7.67 (m, 15 H), 3.70 (ddd, J = 15.6, 11.0, 11.0 Hz, 1 H), 3.52 (dd, J = 7.6, 1.7 Hz, 1 H), 3.45 (apparent t, J = 15.4 Hz, 1 H), 2.08-1.97 (m, 1 H), 1.70-1.62 (m, 1 H), 1.51 (9 lines, J = 6.5 Hz, 1

H), 1.09-0.97 (m, 2 H), 0.850 (s, 9 H), 0.79 (d, J = 6.7 Hz, 3 H), 0.77 (d, J = 7.9 Hz, 3 H), 0.74 (d, J = 6.5 Hz, 3 H), 0.68 (d, J = 6.8 Hz, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 135.2 (J_{cp} = 2.7 Hz), 133.6 (J_{cp} =9.9 Hz), 130.6 (J_{cp} = 12.4 Hz), 118.5 (J_{cp} = 85.5 Hz), 80.1 (J_{cp} = 12.9 Hz), 43.5, 33.6, 32.6 (J_{cp} = 3.7 Hz), 26.2, 25.3 (J_{cp} = 51.1 Hz), 25.0, 23.4, 21.7, 18.6, 18.5, 13.7, -2.7, -3.8; high resolution mass spectrum (FAB,NBA) m/z 533.3369 [(M-I)$^+$; calcd for $C_{34}H_{50}OPSi$: 533.3357].

EXAMPLE 43

Olefin (-)-54.

Phosphonium salt (-)-**49** was dried azeotropically with anhydrous benzene and heated at 50 °C under vacuum for 3 h before use. A solution of (-)-**49** (97.7 mg, 0.0917 mmol) in THF (700 μL) was cooled to -78 °C and treated with NaHMDS (1.0 M in THF, 85.5 μL, 0.0855 mmol). The mixture was stirred for 20 min at 0°C, recooled to -78 °C and aldehyde **C** (28.0 mg, 0.0570 mmol) in THF (300 μL) was added. After 10 min at -78 °C and 2 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl (1.0 mL) and extracted with ether (30 mL). The ether solution was washed with water, brine (30 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (2% ethyl acetate/hexane) provided (-)-**56** (50.0 mg, 76% yield) as a colorless oil: $[\alpha]^{23}_D$ -44.9° © 2.09, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2930 (s), 2855 (s), 1615 (m), 1587 (w), 1517 (m), 1463 (s), 1380 (m), 1360 (m), 1320 (m), 1300 (m), 1250 (s), 1170 (m), 1160 (m), 1120-1000 (s, br), 990 (m), 965 (m), 935 (m), 900 (m), 835 (s), 807 (m), 670 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.35 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 5.37 (s, 1 H), 5.27 (dd, J = 11.2, 7.8 Hz, 1 H), 5.19 (apparent t, J = 10.9 Hz, 1 H), 5.08 (d, J = 10.1 Hz, 1 H), 5.06 (d, J = 2.2 Hz, 1 H), 4.68 (apparent t, J = 9.1 Hz, 1

H), 4.08 (dd, J = 11.2, 4.7 Hz, 1 H), 3.78 (s, 3 H), 3.68 (apparent t, J = 10.1 Hz, 1 H), 3.61 (dd, J = 7.1, 1.7 Hz, 1 H), 3.53 (apparent t, J = 2.6 Hz, 1 H), 3.50 (dd, J = 9.9, 1.6 Hz, 1 H), 3.46 (apparent t, J = 11.1 Hz, 1 H), 3.25 (apparent t, J = 5.3 Hz, 1 H), 2.71-2.58 (m, 1 H), 2.68 (dq, J = 12.8, 7.4 Hz, 1 H), 2.62 (dq, J = 12.8, 7.4 Hz, 1 H), 2.50 (m, 1 H), 2.30 (apparent t, J = 12.2 Hz, 1 H), 2.08-2.01 (m, 1 H), 1.98-1.90 (m, 1 H), 1.88 (dqd, J = 7.1, 7.1, 1.7 Hz, 1 H), 1.82 (apparent qt, J = 7.1, 2.6 Hz, 1 H), 1.65 (br d, J = 12.4 Hz, 1 H), 1.62-1.57 (m, 2 H), 1.56 (d, J = 0.4 Hz, 3 H), 1.38 (ddd, J = 13.6, 10.7, 1.5 Hz, 1 H), 1.29-1.22 (apparent t, J = 7.4 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 3 H), 0.94 (d, J = 7.3 Hz, 3 H), 0.930 (d, J = 6.9 Hz, 3 H), 0.925 (d, J = 7.1 Hz, 3 H), 0.90 (s, 18 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.74 (apparent d, J = 6.6 Hz, 6 H), 0.73 (d, J = 6.1 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H), 0.019 (s, 3 H), 0.017 (s, 3 H), 0.013 (s, 3 H), 0.009 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 134.4, 131.9, 131.8, 131.5, 131.4, 127.3, 113.4, 101.0, 83.4, 80.9, 80.4, 78.5, 76.7, 76.5, 74.2, 73.3, 65.5, 55.2, 42.5, 41.9, 38.2, 37.5, 37.1, 35.4, 34.4, 33.8, 26.3, 26.2, 26.0, 25.9, 25.1, 23.2, 18.5, 18.4, 18.12, 18.08, 17.0, 16.6, 15.6, 14.4, 12.7, 12.1, 11.6, 10.9, -2.7, -3.5, -3.66, -3.69, -4.2, -4.5, -4.9, -5.0; high resolution mass spectrum (FAB, NBA) *m/z* 1171.7799 [$(M+Na)^+$; calcd for $C_{63}H_{120}O_8SSi_4Na$: 1171.7781].

EXAMPLE 44

Hydroxy Diene (-)-55.

A solution of the olefin (-)-**54** (49.8 mg, 0.0434 mmol) in CH_2Cl_2 (4.4 mL) was cooled to -78 °C and DIBAL (1.0 M in toluene, 430 μL, 0.430 mmol) was added over 5 min. After 10 min at -78 °C and 30 min at 0 °C, the reaction was

quenched with saturated aqueous Rochelle's salt (500 μL). The mixture was diluted with ether (60 mL), washed with saturated aqueous Rochelle salt, brine (30 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% ethyl acetate/hexane) furnished (-)-**57** (38.0 mg, 88% yield) as a colorless oil: $[\alpha]^{23}_{D}$ -32° © 1.90, $CHCl_3$); IR ($CHCl_3$) 3500 (w, br), 2960 (s), 2935 (s), 2900 (m), 2885 (m), 2860 (s), 1610 (m), 1585 (w), 1510 (m), 1470 (m), 1460 (m), 1400 (m), 1375 (m), 1360 (m), 1300 (m), 1250 (s), 1170 (m), 1095 (m), 1080 (m), 1047 (s), 1000 (m), 960 (m), 950 (m), 933 (m), 835 (s), 805 (m), 665 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.24 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 5.27 (dd, J = 11.4, 7.8 Hz, 1 H), 5.20 (apparent t, J = 10.3 Hz, 1 H), 5.10 (d, J = 10.0 Hz, 1 H), 5.05 (d, J = 2.2 Hz, 1 H), 4.68 (apparent t, J = 9.2 Hz, 1 H), 4.49 (ABq, J_{AB} = 10.4 Hz, $\Delta\delta_{AB}$ = 23.4 Hz, 2 H), 3.78 (s, 3 H), 3.73 (ddd, J = 10.7, 4.0, 4.0 Hz, 1 H), 3.68 (apparent t, J = 10.4 Hz, 1 H), 3.57 (ddd, J = 10.6, 5.1, 5.1 Hz, 1 H), 3.53 (dd, J = 5.4, 3.4 Hz, 1 H), 3.50 (apparent t, J = 5.2 Hz, 1 H), 3.35 (apparent t, J = 5.5 Hz, 1 H), 3.26 (apparent t, J = 5.2 Hz, 1 H), 2.68 (dq, J = 12.8, 7.4 Hz, 1 H), 2.61 (dq, J = 12.8, 7.5 Hz, 1 H), 2.71-2.58 (m, 2 H), 2.51-2.44 (m, 1 H), 2.22 (apparent t, J = 12.4 Hz, 1 H), 1.99-1.86 (m, 3 H), 1.81 (apparent qt, J = 7.1, 2.6 Hz, 1 H), 1.72 (br d, J = 12.7 Hz, 1 H), 1.62-1.57 (m, 1 H), 1.61 (s, 3 H), 1.56-1.48 (m, 1 H), 1.38 (ddd, J = 13.5, 12.3, 1.4 Hz, 1 H), 1.27 (apparent t, J = 7.4 Hz, 3 H), 1.03 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 0.95-0.92 (m, 9 H), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.74 (d, J = 8.0 Hz, 3 H), 0.73 (d, J = 7.0 Hz, 3 H), 0.08 (s, 6 H), 0.05 (s, 3 H), 0.024 (s, 3 H), 0.020 (s, 3 H), 0.012 (s, 3 H), 0.009 (s, 3 H), 0.006 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.4, 134.4, 132.3, 131.7, 130.9, 130.4, 129.3, 114.0, 86.3, 80.9, 80.4, 77.6, 76.5, 75.3, 74.2, 65.6, 65.5, 55.3, 42.6, 41.9, 40.0,

37.6, 37.0, 36.8, 35.9, 35.2, 34.5, 26.30, 26.27, 25.9, 25.8, 25.1, 23.2, 18.53, 18.47, 18.13, 18.07, 17.1, 16.6, 15.7, 15.6, 14.4, 13.6, 11.6, 11.4, -2.8, -3.2, -3.4, -3.6, -4.2, -4.5, -4.9; high resolution mass spectrum (FAB, NBA) *m/z* 1173.7859 [$(M+Na)^+$; calcd for $C_{63}H_{122}O_8SSi_4Na$: 1173.7835].

EXAMPLE 45

Aldehyde (-)-56.

A solution of alcohol (-)-**55** (13.8 mg, 0.0120 mmol) and Et_3N (42 μL, 0.30 mmol) in CH_2Cl_2 (200 μL) was cooled to 0 °C and treated with SO_3.pyridine (40 mg, 0.251 mmol) in DMSO (600 μL). After 45 min at 0 °C, the mixture was diluted with ethyl acetate (30 mL), washed with aqueous $NaHSO_4$ (1.0 M, 30 mL), brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (3% ethyl acetate/hexane) afforded (-)-**56** (13.2 mg, 96% yield) as a colorless oil: $[\alpha]^{23}_D$ -32.1° © 1.40, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2935 (s), 2880 (m), 1720 (m), 1610 (m), 1512 (m), 1470 (m), 1460 (m), 1387 (m), 1380 (m), 1360 (m), 1340 (m), 1320 (m), 1300 (m), 1250 (s), 1110 (s), 1098 (s), 1080 (s), 1048 (s), 1002 (m), 988 (m), 965 (m), 950 (m), 935 (m), 835 (s) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 9.78 (d, *J* = 2.5 Hz, 1 H), 7.20 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 5.27 (dd, *J* = 11.1, 7.8 Hz, 1 H), 5.19 (apparent t, *J* = 10.4 Hz, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 5.05 (d, *J* = 2.1 Hz, 1 H), 4.67 (apparent t, *J* = 8.9 Hz, 1 H), 4.45 (apparent s, 2 H), 3.78 (s, 3 H), 3.68 (apparent t, *J* = 10.2 Hz, 1 H), 3.58-3.56 (m, 2 H), 3.51 (apparent t, *J* = 2.6 Hz, 1 H), 3.25 (apparent t, *J* = 5.2 Hz, 1 H), 2.73 (dqd, *J* = 7.1, 6.0, 2.6 Hz, 1 H), 2.70-2.57 (m, 3 H), 2.51-2.44 (m, 1 H), 2.23 (apparent t, *J* = 12.4 Hz, 1 H), 1.98-1.85 (m, 2 H), 1.81 (apparent qt, *J* = 7.1, 2.6 Hz, 1 H), 1.67 (br d, *J* = 13.0 Hz, 1 H), 1.60 (s, 3 H), 1.62-1.50 (m, 2H), 1.37 (ddd, *J* = 13.8, 10.4, 1.5 Hz, 1 H), 1.26 (apparent t, *J* = 7.4 Hz, 3

H), 1.10 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 0.938 (d, J = 7.1 Hz, 3 H), 0.932 (d, J = 7.8 Hz, 3 H), 0.919 (s, 9 H), 0.918 (d, J = 6.6 Hz, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.732 (d, J = 6.7 Hz, 3 H), 0.726 (d, J = 6.8 Hz, 3 H), 0.07 (s, 3 H), 0.053 (s, 3 H), 0.047 (s, 3 H), 0.02 (s, 6 H), 0.009 (s, 3 H), 0.005 (s, 6 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 204.6, 159.3, 134.4, 132.3, 131.8, 130.8, 130.3, 129.1, 128.3, 113.8, 82.6, 80.9, 80.4, 76.5, 74.5, 74.2, 65.5, 55.3, 49.5, 42.5, 41.9, 40.3, 37.1, 36.8, 35.4, 34.9, 34.4, 26.3, 26.2, 25.9, 25.8, 25.1, 23.2, 18.49, 18.45, 18.12, 18.07, 17.0, 16.6, 15.6, 14.4, 13.3, 12.1, 11.6, 11.4, -2.8, -3.3, -3.4, -3.7, -4.2, -4.5, -4.9, -5.0; high resolution mass spectrum (FAB, NBA) m/z 1171.7670 [$(M+Na)^+$; calcd for $C_{63}H_{120}O_8SSiNa$: 1171.7676].

EXAMPLE 46

Tetraene (-)-57.

A solution of $Ph_2PCH_2CH=CH_2$ (40 μL, 0.19 mmol) in THF (1.0 mL) was cooled to -78 °C and t-BuLi (1.7 M in pentane, 72.0 μL, 0.122 mmol) was added. The mixture was stirred at 0 °C for 30 min, recooled to -78 °C and treated with $Ti(O\textit{i}Pr)_4$ (45 μL, 0.15 mmol). After 30 min, a cold (-78 °C) solution of the aldehyde (-)-**56** (30.2 mg, 0.0262 mmol) in THF (1.0 mL) was introduced via cannula, and the resultant mixture was stirred for 10 min at -78 °C and 1 h at 0 °C. MeI (20 μL, 0.32 mmol) was then added, and the reaction was maintained at 0 °C for 30 min, warmed to room temperature, protected from light with aluminum foil, and stirred overnight. The reaction mixture was diluted with ether (30 mL), washed with aqueous $NaHSO_4$ (1.0 M), brine (30 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (2% ethyl acetate/hexane) gave a 16:1 mixture of Z/E isomers (20.0 mg, 70% yield) as an oil. Pipette flash chromatography (20% benzene/hexane) furnished the Z-olefin (-)-**57** as a colorless oil: $[\alpha]^{23}_D$ -57.2° © 2.56,

$CHCl_3$); IR ($CHCl_3$) 3015 (m), 2960 (s), 2940 (s), 2900 (m), 2885 (m), 2860 (s), 1613 (w), 1515 (m), 1475 (m), 1465 (m), 1390 (w), 1380 (w), 1360 (w), 1250 (s), 1110 (m), 1100 (m), 1080 (m), 1050 (s), 1003 (m), 963 (w), 950 (w), 835 (s), 800 (m), 790 (m), 770 (m), 700 (w), 690 (w), 670 (w), 655 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.25 (d, J = 8.2 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.57 (dddd, J = 16.8, 11.0, 11.0, 0.7 Hz, 1 H), 6.00 (apparent t, J = 11.1 Hz, 1 H), 5.55 (apparent t, J = 10.5 Hz, 1 H), 5.26 (dd, J = 11.2, 7.8 Hz, 1 H), 5.20-5.16 (m, 2 H), 5.09 (d, J = 10.1 Hz, 1 H), 5.05 (d, J = 2.2 Hz, 1 H), 5.03 (d, J = 10.0 Hz, 1 H), 4.67 (apparent t, J = 9.1 Hz, 1 H), 4.49 (ABq, J_{AB} = 10.6 Hz, $\Delta\delta_{AB}$ = 41.3 Hz, 2 H), 3.78 (s, 3 H), 3.68 (apparent t, J = 10.2 Hz, 1 H), 3.52 (apparent t, J = 2.6 Hz, 1 H), 3.43 (dd, J = 4.8, 3.9 Hz, 1 H), 3.24-3.21 (m, 2 H), 3.01-2.94 (m, 1 H), 2.67 (dq, J = 12.8, 7.4 Hz, 1 H), 2.61 (dq, J = 12.8, 7.5 Hz, 1 H), 2.71-2.57 (m, 1 H), 2.46-2.39 (m, 1 H), 2.00 (apparent t, J = 12.4 Hz, 1 H), 1.83-1.73 (m, 3 H), 1.64 (br d, J = 14.0 Hz, 1 H), 1.62-1.52 (m, 2 H), 1.55 (d, J = 0.5 Hz, 3 H), 1.36 (ddd, J = 13.7, 10.8, 1.5 Hz, 1 H), 1.26 (d, J = 7.4 Hz, 3 H), 1.25 (d, J = 7.4 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 7.1 Hz, 3 H), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.89-0.86 (m, 3 H), 0.86 (s, 9 H), 0.73 (d, J = 6.8 Hz, 3 H), 0.70 (d, J = 6.7 Hz, 3 H), 0.08 (s, 6 H), 0.05 (s, 3 H), 0.02 (s, 3 H), 0.013 (s, 3 H), 0.010 (s, 6 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.1, 134.5, 134.3, 132.2, 131.9, 131.8, 131.2, 129.13, 129.07, 117.6, 113.7, 84.6, 80.9, 80.5, 76.5, 75.0, 74.2, 65.5, 55.3, 42.5, 41.9, 40.2, 37.2, 36.1, 35.4, 35.3, 34.5, 29.7, 26.3, 26.0, 25.9, 25.1, 23.1, 18.7, 18.6, 18.5, 18.14, 18.09, 17.0, 16.8, 15.6, 14.8, 14.4, 11.6, 10.6, -2.8, -3.2, -3.3, -3.6, -4.2, -4.5, -4.90, -4.93; high resolution mass spectrum (FAB, NBA) m/z 1195.8001 [$(M+Na)^+$; calcd for $C_{66}H_{124}O_7SSi_4Na$: 1195.8042].

EXAMPLE 47

Lactone (-)-58.

A solution of diene (-)-**57** (7.0 mg, 0.00597 mmol) in THF/CH_3CN (2:1, 1.50 mL) was treated with pH 7.0 phosphate buffer (500 μL) and $HgCl_2$ (215 mg). The suspension was stirred at room temperature for 40 min, diluted with ether (30 mL), washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (5% ethyl acetate/hexane) provided a mixture of lactols as a colorless oil which was further treated with DMSO (1.0 mL) and Ac_2O (200 mL) at room temperature for 2 days. The mixture was diluted with ether (30 mL), washed with saturated $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (2% ethyl acetate/hexane) provided (-)-**58** (5.5 mg, 82% yield from (-)-**57**) as a colorless oil: $[\alpha]^{23}_{D}$ -31.6 © 0.23, $CHCl_3$); IR ($CHCl_3$) 3015 (m), 2960 (s), 2930 (s), 2880 (m), 2855 (m), 1725 (m), 1610 (w), 1510 (w), 1460 (m),1385 (m), 1373 (m), 1360 (m), 1300 (w), 1250 (s), 1230 (m), 1200 (m), 1170 (m), 1120 (m), 1097 (m), 1060 (m), 1045 (s), 1020 (m), 1003 (m), 980 (w), 955 (w), 930 (w), 905 (w), 867 (m), 835 (s), 800 (m), 695 (m), 670 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 7.25 (d, J = 9.0 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.57 (ddd, J = 16.7, 10.6, 10.6 Hz, 1 H), 6.00 (apparent t, J = 11.0 Hz, 1 H), 5.55 (apparent t, J = 10.5 Hz, 1 H), 5.26 (dd, J = 11.1, 7.9 Hz, 1 H), 5.19 (dd, J = 15.4, 1.4 Hz, 1 H), 5.18 (apparent t J = 10.1 Hz, 1 H), 5.10 (d, J = 10.2 Hz, 1 H), 5.01 (d, J = 10.0 Hz, 1 H), 4.75 (apparent t, J = 9.2 Hz, 1 H), 4.50 (ddd, J = 10.5, 1.3, 1.3 Hz, 1 H), 4.50 (ABq, J_{AB} = 10.6 Hz, $\Delta\delta_{AB}$ = 42.6 Hz, 2 H), 3.78 (s, 3 H), 3.60 (apparent t, J = 2.4 Hz, 1 H), 3.42 (dd, J = 5.1, 3.7 Hz, 1 H), 3.23 (dd, J = 7.5, 3.7 Hz, 1 H), 3.20 (apparent t, J = 5.4 Hz, 1 H), 3.01-2.94 (m, 1 H), 2.60 (qd, J = 7.7, 2.6 Hz,

1 H), 2.62-2.55 (m, 1 H), 2.45-2.38 (m, 1 H), 1.98 (apparent t, J = 12.3 Hz, 1 H), 1.84-1.67 (m, 3 H), 1.63 (br d, J = 13.2 Hz, 1H), 1.52 (s, 3 H), 1.55-1.48 (m, 1 H), 1.20 (d, J = 7.6 Hz, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.93 (apparent d, J = 6.7 Hz, 6 H), 0.93 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.85 (s, 9 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.69 (d, J = 6.7 Hz, 3 H), 0.085 (s, 3 H), 0.079 (s, 3 H), 0.051 (s, 3 H), 0.046 (s, 3 H), 0.042 (s, 3 H), 0.029 (s, 3 H), 0.028 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.2, 159.1, 134.4, 133.4, 132.4, 132.2, 131.9., 131.3, 131.2, 129.11, 129.09, 117.6, 113.7, 84.6, 80.5, 76.9, 75.0, 74.9, 64.6, 55.3, 44.1, 42.7, 40.1, 37.5, 36.0, 35.44, 35.37, 35.2, 34.2, 26.31, 26.28, 25.9, 25.7, 23.0, 18.7, 18.6, 18.4, 18.1, 18.0, 17.1, 16.5, 16.4, 14.9, 14.1, 10.5, -3.0, -3.2, -3.3, -4.3, -4.4, -4.5, -4.8, -4.9; high resolution mass spectrum (FAB, NBA) *m/z* 1149.7836 [$(M+Na)^+$; Calcd for $C_{64}H_{118}O_8Si_4Na$: 1149.7802].

EXAMPLE 48

Alcohol (-)-59.

A solution of (-)-**58** (4.0 mg, 0.00355 mmol) in CH_2Cl_2 (500 μL) was treated with H_2O (50 μL) and DDQ (3.0 mg, 0.0132 mmol) at 0 °C. After 1 h, the mixture was diluted with ethyl acetate (30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (2% ethyl acetate/hexane) provided (-)-**59** (3.4 mg, 95% yield) as a colorless oil: $[\alpha]^{23}_{D}$ -20° © 0.34, $CHCl_3$); IR (film, $CHCl_3$ on NaCl plate) 3500 (w, br), 2960 (s), 2930 (s), 2890 (s), 2855 (s), 1740 (m), 1460 (m), 1405 (m), 1380 (m), 1360 (s), 1253 (m), 1220 (m), 1120 (s), 1093 (s), 1075 (s), 1045 (s), 1022 (s), 1002 (m), 980 (m), 933 (m), 902 (m), 833 (s), 808 (m), 770 (s), 663 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 6.61 (ddd, J = 16.8, 10.9, 10.9 Hz, 1 H), 6.13 (apparent t, J = 11.0 Hz, 1 H), 5.32 (apparent t, J =

10.5 Hz, 1 H), 5.28 (dd, J = 11.1, 7.9 Hz, 1 H), 5.24-5.21 (m, 1 H), 5.19 (apparent t, J = 10.3 Hz, 1 H), 5.14 (d, J = 10.2 Hz, 1 H), 5.06 (d, J = 10.0 Hz, 1 H), 4.76 (apparent t, J = 9.3 Hz, 1 H), 4.50 (apparent t, J = 9.9 Hz, 1 H), 3.62 (apparent t, J = 2.4 Hz, 1 H), 3.60 (dd, J = 5.5, 3.4 Hz, 1 H), 3.32 (br d, J = 5.3 Hz, 1 H), 3.24 (apparent t, J = 5.1 Hz, 1 H), 2.79 (ddq, J = 9.9, 6.7, 6.7 Hz, 1 H), 2.60 (qd, J = 7.6, 2.7 Hz, 1 H), 2.63-2.57 (m, 1 H), 2.50-2.45 (m, 1 H), 2.16 (apparent t, J = 12.3 Hz, 1 H), 1.90-1.77 (m, 3 H), 1.75-1.69 (m, 2 H), 1.57 (s, 3 H), 1.60-1.50 (m, 1 H), 1.20 (d, J = 7.6 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.95-0.93 (m, 6 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.89-0.84 (m, 3 H), 0.87 (s, 9 H), 0.85 (s, 9 H), 0.73 (d, J = 6.8 Hz, 3 H), 0.07 (apparent s, 6 H), 0.052 (s, 3 H), 0.051 (s, 3 H), 0.04 (apparent s, 6 H), 0.03 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.3, 134.7, 133.5, 132.5, 132.1, 132.0, 131.5, 131.0, 118.4, 80.5, 78.8, 76.4, 74.9, 64.7, 44.1, 42.7, 38.0, 37.4, 36.3, 36.1, 35.2, 35.1, 34.2, 26.3, 26.2, 25.9, 25.7, 23.2, 18.5, 18.1, 18.0, 17.3, 17.2, 16.4, 16.1, 14.1, 13.7, 9.4, -3.0, -3.3, -3.6, -4.34, -4.36, -4.5, -4.8; high resolution mass spectrum (FAB, NBA) *m/z* 1029.7273 [$(M+Na)^+$; calcd for $C_{56}H_{110}O_7Si_4Na$: 1029.7226].

EXAMPLE 49

Carbamate (-)-60.

A solution of alcohol (-)-**59** (2.2 mg, 0.00219 mmol) in CH_2Cl_2 (500 μL) was treated with $Cl_3CON{=}C{=}O$ (20 μL, 0.168 mmol) at room temperature. After 30 min, the mixture was diluted with regular CH_2Cl_2 (2.0 mL) and treated with neutral Al_2O_3 (500 mg). The mixture was stirred at room temperature for 2 h, filtered through a short silica plug, and concentrated. Pipette flash chromatography (10% ethyl acetate/hexane) provided (-)-**60** (1.9 mg, 83% yield) as a

colorless oil: $[\alpha]^{23}_{D}$ -37° © 0.19, $CHCl_3$); IR (film, $CHCl_3$ on NaCl plate) 3510 (m), 3360 (m, br), 3180 (m), 2960 (s), 2930 (s), 2880 (s), 2855 (s), 1730 (s, br), 1596 (m), 1460 (s), 1385 (s), 1362 (s), 1325 (m), 1255 (s), 1220 (m), 1100 (s), 1043 (s), 983 (m), 937 (m), 904 (m), 832 (s), 770 (s), 663 (m) cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$) d 6.58 (dddd, *J* = 16.8, 10.6, 10.6, 0.7 Hz, 1 H), 6.01 (apparent t, *J* = 11.0 Hz, 1 H), 5.36 (apparent t, *J* = 10.4 Hz, 1 H), 5.27 (dd, *J* = 11.1, 7.9 Hz, 1 H), 5.22-5.16 (m, 2 H), 5.12 (d, *J* = 10.1 Hz, 1 H), 5.03 (d, *J* = 10.0 Hz, 1 H), 4.76 (apparent t, *J* = 9.2 Hz, 1 H), 4.71 (apparent t, *J* = 6.1 Hz, 1 H), 4.50 (ddd, *J* = 10.5, 10.5, 1.3 Hz, 1 H), 4.44 (br s, 2 H), 3.62 (apparent t, *J* = 2.4 Hz, 1 H), 3.42 (apparent t, *J* = 4.5 Hz, 1 H), 3.22 (apparent t, *J* = 5.3 Hz, 1 H), 2.98 (ddq, *J* = 10.1, 6.6, 6.6 Hz, 1 H), 2.60 (qd, *J* = 7.6, 2.7 Hz, 1 H), 2.63-2.55 (m, 1 H), 2.48-2.41 (m, 1 H), 2.09 (apparent t, *J* = 12.4 Hz, 1 H), 1.93-1.88 (m, 1 H), 1.87-1.77 (m, 2 H), 1.71 (ddd, *J* = 14.1, 10.8, 1.6 Hz, 1 H), 1.67 (br d, *J* = 13.7 Hz, 1 H), 1.56 (apparent s, 3 H), 1.55-1.50 (m, 1 H), 1.21 (d, *J* = 7.6 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.94 (d, *J* = 7.5 Hz, 3 H), 0.918 (d, *J* = 6.8 Hz, 3 H), 0.915 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.853 (d, *J* = 6.4 Hz, 3 H), 0.847 (s, 9 H), 0.70 (d, *J* = 6.8 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.053 (s, 3 H), 0.051 (s, 3 H), 0.040 (s, 3 H), 0.037 (s, 3 H), 0.03 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.3, 156.9, 133.6, 133.5, 132.4, 132.1, 131.9, 131.4, 129.8,118.0, 80.5, 78.9, 74.9, 64.6, 44.2, 42.7, 37.8, 37.4, 36.0, 35.3, 35.2, 34.5, 34.2, 26.3, 26.2, 25.9, 25.7, 23.0, 18.5, 18.4, 18.1, 18.0, 17.5, 17.1, 16.44, 16.38, 14.1, 13.7, 10.1, -3.0, -3.4, -3.6, -4.4, -4.5, -4.8; high resolution mass spectrum (FAB, NBA) *m/z* 1072.7264 [$(M+Na)^+$; calcd for $C_{57}H_{111}NO_8Si_4Na$: 1072.7283].

EXAMPLE 50

Discodermolide [(-)-1].

A solution of olefin (-)-**60** (5.8 mg, 5.5 mmol) in 48% HF-CH_3CN (1:9, 1.0 mL) was stirred at room temperature for 12 h, then quenched with saturated aqueous $NaHCO_3$ (5.0 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (5.0 mL), dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (gradient elution, 1:30 to 1:6 MeOH/$CHCl_3$) provided (-)-1 (2.0 mg, 60% yield) as a white amorphous solid: $[\alpha]^{23}_D$ -16° © 0.03, MeOH); IR ($CHCl_3$) 3690 (w), 3620 (w), 3540 (w), 3430 (w), 3020 (s), 2975 (m), 2935 (m), 1740 (m), 1590 (w), 1540 (w), 1520 (w), 1467 (w), 1430 (w), 1385 (m), 1330 (w), 1233 (s), 1210 (s), 1100 (w), 1045 (m), 1033 (m), 975 (w), 930 (m), 910 (w), 793 (m), 777 (m), 765 (m), 750 (m), 705 (m), 687 (m), 670 (m), 660 (m), 625 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 6.60 (dddd, J = 16.8, 8.4, 8.4, 0.8 Hz, 1 H), 6.02 (apparent t, J = 11.1 Hz, 1 H), 5.51 (dd, J = 11.2, 7.9 Hz, 1 H), 5.42 (ddd, J = 10.6, 10.6, 0.6 Hz, 1 H), 5.34 (apparent t, J = 10.4 Hz, 1 H), 5.20 (dd, J = 16.9, 1.9 Hz, 1 H), 5.16 (d, J = 10.0 Hz, 1 H), 5.11 (d, J = 10.1 Hz, 1 H), 4.77-4.69 (m, 1 H), 4.70 (dd, J = 7.3, 4.2 Hz, 1 H), 4.60 (ddd, J = 10.0, 10.0, 2.4 Hz, 1 H), 4.56 (br s, 2 H), 3.73 (m, 1 H), 3.28 (m, 1 H), 3.18 (dd, J = 6.8, 4.8 Hz, 1 H), 2.98 (ddq, J = 10.1, 6.9, 6.9 Hz, 1 H), 2.78 (ddq, J = 9.8, 6.8, 6.8 Hz, 1 H), 2.66 (qd, J = 7.3, 4.6 Hz, 1 H), 2.60-2.55 (m, 1 H), 2.10-1.80 (m, 10 H), 1.69 (ddd, J = 14.4, 10.3, 3.1 Hz, 1 H), 1.64 (d, J = 1.3 Hz, 3 H), 1.30 (d, J = 7.4 Hz, 3 H), 1.06 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.6, 157.0, 134.4, 133.7, 133.4, 132.9, 132.2, 129.9, 129.8, 117.9, 79.1, 78.9, 77.9,

75.7, 73.2, 64.4, 43.1, 41.0, 37.4, 36.1, 36.0, 35.8, 35.3, 34.8, 33.1, 23.3, 18.4, 17.4, 15.6, 15.5, 13.7, 12.5, 9.0; high resolution mass spectrum (FAB, NBA) *m/z* 616.3840 [$(M+Na)^+$; calcd for $C_{33}H_{55}NO_8Na$: 616.3826].

EXAMPLE 51 (Figures 16 and 17)

A. Tosylate 101

A solution of diene 16 (*see*, Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) (1.15 g, 1.0 mmol) in anhydrous pyridine (10 mL) at 0 °C is treated with p-toluenesulfonyl chloride (286 mg, 1.5 mmol). The mixture is allowed to warm to room temperature for 4-6 h. The pyridine is removed *in vacuo* and the residue is purified by flash chromatography to afford tosylate 101.

B. Arene 102

Phenyllithium (2.7 mL, 1.8 M in cyclohexane-ether (70:30)) is added dropwise to a solution of copper (I) iodide (460 mg, 2.4 mmol) in anhydrous diethyl ether (5 mL) at 0 °C. To the resultant mixture is added a solution of tosylate 101 (780 mg, 0.6 mmol) in ether (5 mL) and the resultant mixture is warmed to room temperature with stirring. After 4 h, saturated aqueous ammonium chloride (20 mL) is added. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organics are dried over magnesium sulfate and concentrated *in vacuo.* The residue is purified by flash chromatography to afford 102.

C. Lactol 103.

To a solution of 102 (120 mg, 0.1 mmol) in tetrahydrofuran-acetonitrile (15 mL, 2:1) is added phosphate buffer (pH 7, 5 mL) and mercury (II) chloride (272 mg, 1.0 mmol). The resultant mixture is stirred 1 h at room temperature. The reaction mixture is diluted with ether (100 mL) and washed with saturated aqueous brine (2 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo.* The residue is purified by flash chromatography to afford

103 as a mixture of α and β anomers.

D. Lactone 104.

To a solution of 103 (84 mg, 0.070 mmol) in dimethyl sulfoxide (10 mL) is added acetic anhydride (2 mL). After 2 days at room temperature, the mixture is diluted with ether (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), saturated aqueous brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 104.

E. Alcohol 105.

To a solution of 104 (56 mg, 0.050 mmol) in dichloromethane (3 mL) at 0 °C is added water (50 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (52 mg, 0.018 mmol). After 1 h, the reaction mixture is diluted with ethyl acetate (50 mL), washed with saturated aqueous brine (3 x 25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 105.

F. Carbamate 106.

To a solution of 105 (10 mg, 0.010 mmol) in dichloromethane (2 mL) is added trichloroacetyl isocyanate (0.12 mL, 1.00 mmol). After 30 min, the reaction mixture is diluted with dichloromethane (4 mL) and neutral alumina (1 g) is added. The resultant suspension is stirred an additional 4 h. The reaction mixture is filtered and the concentrated filtrate is chromatographed on silica gel to afford 106.

G. Tetrol 107.

A solution of 106 (10 mg, 0.0096 mmol) in 48% hydrofluoric acid-acetonitrile (1:9, 2 mL) is stirred at ambient temperature. After 12 h, saturated aqueous sodium bicarbonate (25 mL) is added and the mixture is extracted with ethyl acetate (3 x 20 mL). The combined organics are dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 107.

EXAMPLE 52 (Figures 18-20)

A. Alcohol 203.

To a slurry of powdered 4-Å molecular sieves (2.0 g) in 100 mL of anhydrous toluene is added boronate 202 (*see*, Roush, *et al.*, *J. Am. Chem. Soc.* **1990**, *112*, 6348) (170 mL, 1.0 M in toluene). The resultant solution is stirred 10 min at room temperature and then cooled to - 78 °C. A solution of aldehyde 201 (*see*, Solladie, *et al.*, *Tetrahedron Lett.* **1987**, *28*, 797) (113 mmol) in toluene (100 mL) is added over a 2 h period, after which the reaction is maintained at -78 °C for 10 h. Excess ethanolic sodium borohydride (ca. 0.75 g/10 mL) is added and the reaction mixture is warmed to 0 °C. Aqueous 1 N sodium hydroxide (300 mL) is added and the mixture is stirred vigorously for 2 h. The layers are separated and the aqueous layer is extracted with ether (5 x 300 mL). The combined organics are dried over potassium carbonate and concentrated *in vacuo.* The residue is purified by flash chromatography to afford 203.

B. Bis-silyl ether 204

A solution of 203 (75 mmol) in dimethylformamide (150 mL) is cooled to 0 °C and treated with imidazole (150 mmol) and tert-butyldimethylsilyl chloride (100 mmol). The resultant solution is warmed to room temperature. After 12 h, the reaction mixture is poured into 1500 mL of water and extracted with ether (3 x 200 mL). The ethereal extracts are washed with water (2 x 50 mL) and saturated aqueous brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo.* The residue is purified by flash chromatography to afford 204.

C. Alcohol 205.

A solution of 204 (20 mmol) in 500 mL of methanol is cooled to -78 °C and treated with a stream of ozone and oxygen until the colorless solution is converted into a steel blue one. The crude reaction mixture is cautiously quenched with sodium borohydride (100 mmol) and the

resultant solution is warmed to room temperature. After 3 h, the excess sodium borohydride is destroyed by the cautious addition of water. The methanol is removed *in vacuo* and the residue is partitioned between saturated aqueous ammonium chloride (200 mL) and ethyl acetate (200 mL). The layers are separated and the aqueous layer is further extracted with ethyl acetate (2 x 100 mL). The combined organics are dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 205.

D. Triethylsilyl ether 206.

A solution of 205 (15 mmol) in dimethylformamide (30 mL) is cooled to 0 °C and treated with imidazole (30 mmol) and triethylsilyl chloride (20 mmol). The resultant solution is warmed to room temperature. After 12 h, the reaction mixture is poured into 300 mL of water and extracted with ether (3 x 40 mL). The ethereal extracts are washed with water (2 x 25 mL) and saturated aqueous brine (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 206.

E. Alcohol 207.

To a solution of 206 (6 mmol) in ethyl acetate-ethanol (8:1, 90 mL) is added palladium on carbon (10% wet, 500 mg). The mixture is stirred under hydrogen atmosphere for 3-6 h, then filtered and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 207.

F. Aldehyde 208.

To a -10 °C solution of 207 (13 mmol) and triethylamine (50 mmol) in dichloromethane (26 mL) is added a solution of sulfur trioxide-pyridine (39 mmol) in dimethyl sulfoxide (50 mL). The mixture is stirred 1 h at room temperature and diluted with ether (150 mL). The organic phase is washed with aqueous sodium bisulfate (1 M, 100 mL), saturated aqueous brine (4 x 100 mL), dried over magnesium

sulfate, and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 208.

G. Wittig product 209.

Phosphonium salt 15 (*see*, Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) (0.2 mmol) is dissolved in anhydrous tetrahydrofuran (2 mL) and chilled to 0 °C. A solution of sodium bis(trimethylsilyl)amide (0.2 mmol, 1.0 M in tetrahydrofuran) is added and the reaction mixture is stirred 30 min at 0 °C. After cooling to -78 °C, a solution of aldehyde 208 (0.1 mmol) in tetrahydrofuran (2 mL) is added and the mixture is stirred 10 min at -78 °C and 2 h at room temperature. Saturated aqueous ammonium chloride (2 mL) is added and the resultant mixture is extracted with ether (3 x 20 mL). The ethereal layer is washed with water (2 x 25 mL) and saturated aqueous brine (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 209.

H. Hydroxy diene 210.

A -78 °C solution of 209 (0.05 mmol) in CH_2Cl_2 (5 mL) is treated with diisobutylaluminum hydride (0.5 mL, 1.0 M in toluene). The resultant solution is stirred 10 min at -78 °C and 30 min at 0 °C. The reaction is quenched with a saturated solution of sodium potassium tartrate (50 mL) and the mixture is diluted with ether (60 mL). The organic layer is separated, dried over magnesium sulfate, and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 210.

I. Aldehyde 211.

To a -10 °C solution of 207 (1.3 mmol) and triethylamine (5.0 mmol) in dichloromethane (3 mL) is added a solution of sulfur trioxide-pyridine (3.9 mmol) in dimethyl sulfoxide (5 mL). The mixture is stirred 1 h at room temperature and diluted with ether (15 mL). The organic phase is washed with aqueous sodium bisulfate (1 M, 10 mL), saturated aqueous brine (4 x 10 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue

is purified by flash chromatography to afford 211.

J. Tetraene 212.

A solution of diphenylallylphosphine (0.08 mL, 0.38 mmol) in tetrahydrofuran (2 mL) is cooled to -78 °C and tert-butyllithium (0.14 mL, 1.7 M in pentane) is added. The mixture is warmed to 0 °C for 30 min, then recooled to -78 °C and treated with titanium (IV) isopropoxide (0.30 mmol). After 30 min, aldehyde 211 (0.30 mmol) is introduced as a solution in tetrahydrofuran (2 mL). The resultant solution is stirred at -78 °C for 15 min and at 0 °C for 1 h. Methyl iodide (0.64 mmol) is added, and the reaction is warmed to room temperature for 12 h. The reaction mixture is diluted with ether (60 mL), washed with aqueous sodium bisulfate (30 mL, 1.0 M), saturated aqueous brine (30 mL), and is dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 212.

K. Aldehyde 213.

Oxalyl chloride (1.5 mmol) is added dropwise to a -78 °C solution of dimethyl sulfoxide (3 mmol) in dichloromethane (4 mL). After 15 min, a -78 °C solution of 212 (1 mmol) in dichloromethane (2 mL) is added via canula. After an additional 15 min, diisopropylethylamine (4.5 mmol) is added and the reaction is gradually warmed to room temperature over 1 h and quenched with aqueous sodium bisulfate. The mixture is diluted with ether (50 mL) and is washed with water (2 x 30 mL), saturated aqueous brine (2 x 30 mL), is dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 213.

L. Ester 214.

To a -78 °C solution of $(F_3CCH_2O)_2POCH_2CO_2Et$ (2 mmol) and 18-crown-6 (2.4 mmol) in tetrahydrofuran (5 mL) is added potassium bis(trimethylsilyl)amide (2 mmol) in tetrahydrofuran (2 mL). The resultant solution is stirred 10 min at -78 °C and then treated with aldehyde 213 (1.2 mmol) in 4 mL of tetrahydrofuran. The reaction mixture is warmed to 0 °C for 6-8 h and then quenched with saturated

aqueous ammonium chloride (10 mL). The aqueous layer is separated and extracted with hexane (2 x 25 mL). The combined organics are dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 214.

M. Alcohol 215.

To a solution of 214 (0.050 mmol) in dichloromethane (3 mL) at 0 °C is added water (50 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.018 mmol). After 1 h, the reaction mixture is diluted with ethyl acetate (50 mL), washed with saturated aqueous brine (3 x 25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 215.

N. Carbamate 216.

To a solution of 215 (0.010 mmol) in dichloromethane (2 mL) is added trichloroacetyl isocyanate (1.00 mmol). After 30 min, the reaction mixture is diluted with dichloromethane (4 mL) and neutral alumina (1 g) is added. The resultant suspension is stirred an additional 4 h. The reaction mixture is filtered and the concentrated filtrate is chromatographed on silica gel to afford 216.

O. Triol 217.

A solution of 216 (0.010 mmol) in 48% hydrofluoric acid-acetonitrile (1:9, 2 mL) is stirred at ambient temperature. After 12 h, saturated aqueous sodium bicarbonate (25 mL) is added and the mixture is extracted with ethyl acetate (3 x 20 mL). The combined organics are dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 217.

EXAMPLE 53 (Figures 21 and 22)

A. Hydroxy-oxazole 302.

A solution of oxazole (3 mmol) in tetrahydrofuran (15 mL) is cooled to -78 °C and treated with n-BuLi (3 mmol) in hexane. (*see*, Hodges, *et al.*, *J. Org. Chem.* **1991**, *56*,

449). After 30 min at -78 °C, previously prepared (*see*, Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) aldehyde 301 (2 mmol) is added in tetrahydrofuran (10 mL) and the reaction mixture is gradually allowed to warm to room temperature. After 18-24 h, the reaction is quenched by addition of saturated aqueous ammonium chloride (25 mL). The aqueous layer is separated and extracted with ether (3 x 25 mL). The combined organics are dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 302.

B. Tosylate 303.

A solution of 302 (1.0 mmol) in anhydrous pyridine (10 mL) at 0 °C is treated with p-toluenesulfonyl chloride (286 mg, 1.5 mmol). The mixture is allowed to warm to room temperature for 4-6 h. The pyridine is removed *in vacuo* and the residue is purified by flash chromatography to afford tosylate 303.

C. Reduction product 304.

To a 0 °C solution of tosylate 303 (0.5 mmol) in tetrahydrofuran (2 mL) is added lithium triethylborohydride (2 mmol) as a solution in tetrahydrofuran (1.0 M). The resultant solution is warmed to room temperature for 2-4 h and then quenched with water (1 mL) and diluted with ether (25 mL). The ethereal layer is washed with saturated aqueous brine (2 x 10 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 304.

D. Lactol 305.

To a solution of 304 (0.1 mmol) in tetrahydrofuran-acetonitrile (15 mL, 2:1) is added phosphate buffer (pH 7, 5 mL) and mercury (II) chloride (1.0 mol). The resultant mixture is stirred 1 h at room temperature. The reaction mixture is diluted with ether (100 mL) and washed with saturated aqueous brine (2 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 305 as a mixture

of α and β anomers.

E. Lactone 306.

To a solution of 305 (0.070 mmol) in dimethyl sulfoxide (10 mL) is added acetic anhydride (2 mL). After 2 days at room temperature, the mixture is diluted with ether (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), saturated aqueous brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 306.

F. Alcohol 307.

To a solution of 306 (0.050 mmol) in dichloromethane (3 mL) at 0 °C is added water (50 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.018 mmol). After 1 h, the reaction mixture is diluted with ethyl acetate (50 mL), washed with saturated aqueous brine (3 x 25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 307.

G. Carbamate 308.

To a solution of 307 (0.010 mmol) in dichloromethane (2 mL) is added trichloroacetyl isocyanate (1.00 mmol). After 30 min, the reaction mixture is diluted with dichloromethane (4 mL) and neutral alumina (1 g) is added. The resultant suspension is stirred an additional 4 h. The reaction mixture is filtered and the concentrated filtrate is chromatographed on silica gel to afford 308.

H. Tetrol 309.

A solution of 308 (0.010 mmol) in 48% hydrofluoric acid-acetonitrile (1:9, 2 mL) is stirred at ambient temperature. After 12 h, saturated aqueous sodium bicarbonate (25 mL) is added and the mixture is extracted with ethyl acetate (3 x 20 mL). The combined organics are dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 309.

EXAMPLE 54

As shown in Figure 23, a solution of 402 (10.5 mg, 10.4 mmol) in 48% HF-CH_3CN (1:9, 1.0 mL) is stirred at room temperature for 12 hr. The reaction is quenched by saturated $NaHCO_3$ (5.0 mL). The mixture is extracted with ethyl acetate (3 x 10 mL). The combined organic phase is then washed with brine (5.0 mL), dried over $MgSO_4$, concentrated *in vacuo*. The residue is purified by flash chromatography to afford 401.

EXAMPLE 55 (Figure 24)

A. PMB-ether 503

$ZnCl_2$(1.32 g, 9.69 mmol) is dried at 160°C under vacuum overnight and then treated with a solution of iodide 502 (2.46 g, 9.59 mmol) in dry Et_2O (50 mL). The mixture is stirred at room temperature until most of the $ZnCl_2$ is dissolved and then cooled to -78°C. t-BuLi (1.7M in pentane, 17.0 mL) is added over 30 min, and the resultant solution is stirred an additional 15 min, warmed to room temperature, and stirred for 1hr. The solution is added by cannula to a mixture of iodoolefin B (*see*, Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) (3.21 g, 6.19 mmol) and $Pd(PPh_3)_4$ (364.2 mg, 0.315 mmol). The mixture is covered with aluminum foil, stirred overnight, and then diluted with ethyl acetate(100 mL), washed with brine (2 X 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 503.

B. Phosphonium salt 504

A solution of alcohol 503 (1.70 g, 3.26 mmol) in CH_2Cl_2 (28 mL) is cooled to 0 °C and treated with water (1.3 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (774 mg, 3.41 mmol). The mixture is stirred at 0°C for 5 hr, diluted with CH_2Cl_2 (20 mL), dried over $MgSO_4$, and filtered through a column of silica gel. Following concentration *in vacuo*, the residue is dissolved in ethanol (50 mL) at room temperature, and excess sodium borohydride is added. After 30 min, the

reaction is cooled to 0°C, quenched with saturated aqueous NH_4Cl (50 mL), and concentrated. The residue is then dissolved in CH_2Cl_2(90 mL), and the solution is washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography to afford an alcohol

A solution of this alcohol (400 mg, 1.0 mmol) in dry benzene/ether (1:2, 50 mL) is treated with triphenylphosphine (923 mg, 3.6 mmol) and imidazole (273 mg, 4.0 mmol). After all of the imidazole dissolved, iodine (761 mg, 3.0 mmol) is added with vigorous stirring of the reaction mixture. The mixture is stirred 2 h further and then treated with triethylamine (4 mL). The resultant solution is diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $Na_2S_2O_3$(100 mL), saturated aqueous $NaHCO_3$(100 mL), and brine (2 x 100 mL). The organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. Filtration though silica gel to remove triphenylphosphine oxide, affords an iodide. The iodide was mixed with diisopropylethylamine (0.6 mL, 3.44 mmol) and triphenylphosphine (4.94 g, 18.8 mmol). The mixture is heated at 80 °C for 24 hr, cooled to room temperature, and washed with hexane(2 x 50 mL). The product is isolated by flash chromatography to afford 504.

C. Coupled product 505.

Phosphonium salt 504 (386 mg, 0.5 mmol) is dried azeotropically with dry benzene and heated at 50°C under vacuum for 3 hr before use. It is then dissolved in tetrahydrofuran (3.0 mL). Sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.48 mL, 0.48 mmol) is added at -78°C, and the mixture is stirred for 25 min and then recooled to -78°C. A solution of aldehyde C (*see*, Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) (147 mg, 0.30 mmol) in tetrahydrofuran (1.5 mL) is added, and the mixture is stirred for 10 min at -78°C, and 2 hr at room temperature. The reaction is quenched with saturated

aqueous NH_4Cl (4.0 mL), the resultant mixture is extracted with ether (120 mL), and the ether layer is washed with water (100 mL) and brine(100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography provides olefin 505.

D. Lactone 506.

To a solution of 505 (200 mg, 0.23 mmol) in tetrahydrofuran-acetonitrile (10 mL, 2:1) is added a phosphate buffer solution (pH = 7.0, 3.3 mL), and $HgCl_2$ (1.3 g). The suspension is stirred at room temperature for 40 min, then diluted with ether (150 mL), washed with brine (2 x 70 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography provides a mixture of lactols as α/β anomers. This material is used directly in the next oxidation: Under argon, to a solution of lactols in dimethylsulfoxide (5.0 mL) is added acetic anhydride (1.0 mL). After 2 days at room temperature, the mixture is diluted with ether (150 mL), washed with saturated $NaHCO_3$ (150 mL), brine(150 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography affords a lactone. A solution of the lactone (160 mg, 0.20 mmol) in methanol (4 mL) is treated with pyridinium p-toluenesulfonate (10 mg) and stirred at 40°C for 30 min. The mixture is diluted with ether (80 mL) and washed successively with saturated aqueous $NaHCO_3$ solution (90 mL) and brine (40 mL), and then dried over $MgSO_4$. The organic solution is concentrated *in vacuo*, and the residue is passed through a column of silica gel to provide alcohol 506.

E. Acid 507.

To a solution of alcohol 506 (140 mg, 0.19 mmol) in dimethylformamide (5.0 mL), is added pyridinium dichromate (210 mg, 0.55 mmol). The reaction mixture is stirred at room temperature for 5 hr, and diluted with water (120 mL). The mixture is extracted with ether (3 x 15 mL). The organic solutions are combined and washed with brine (40 mL), and dried over $MgSO_4$. Then it is concentrated *in vacuo*

to give a residue, which is purified by flash chromatography to afford carboxylic acid 507.

F. Amino-amide 508.

To a solution of 507 (60.0 mg, 78.1 mmol) and D-leucine hydrochloride (26.0 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 23 mg, 0.12 mmol) and 1-hydroxybenzotriazole (21.0 mg, 0.14 mmol), followed by diisopropylamine (40 mL, 0.23 mmol). The mixture is stirred at room temperature overnight before addition of 5% $KHSO_4$ solution. The resulting mixture is extracted with ethyl acetate (30 mL). The organic layer is washed with brine (20 mL) and dried over $MgSO_4$, and then concentrated *in vacuo*. The residue is purified by column chromatography to afford 508.

G. Analog 501.

A solution of 508 (52 mg, 59 mmol) in 48% HF-acetonitrile(1:9, 1.0 mL) is stirred at room temperature for 12 hr. The reaction is quenched by saturated $NaHCO_3$(5.0mL). The mixture is extracted with ethyl acetate (3 x 10 mL). The combined organic phase is then washed with brine (5.0 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography provides 501.

EXAMPLE 56 (Figure 25)

A. Diene 603.

Phosphonium salt 15 (98.0 mg, 0.092 mmol) is dried azeotropically with dry benzene and heated at 50°C under vacuum for 3 hr before use. It is then dissolved in tetrahydrofuran (0.7 mL). Sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 86 mL, 0.0855 mmol) is added at -78°C, and the mixture is stirred for 20 min and then recooled to -78°C. A solution of aldehyde 602 (13 mg, 60 mmol) in tetrahydrofuran (300 mL) is added, and the mixture is stirred for 10 min at -78°C, and 2 hr at room temperature. The reaction is quenched with saturated aqueous NH_4Cl (1.0 mL). The resultant mixture is extracted

with ether (30 mL), and the ether layer is washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography provides the coupled product.

A solution of the olefin (39 mg, 44 mmol) in CH_2Cl_2 is cooled to -78°C, diisobutylaluminum hydride (1.0 M in toluene, 440 mL, 0.40 mmol) is added dropwise over 5 min, and the resultant solution is stirred for 10 min at -78°C and 30 min at 0°C. The reaction is quenched with a saturated solution of Rochelle's salt, and the mixture is diluted with ether (60 mL), washed with Rochelle solution, and brine(30 mL each), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography provides alcohol 603.

B. Alkane 604.

To a solution of alcohol 603 (82 mg, 0.93 mmol) in pyridine (1.5 mL) at 0°C is added p-toluenesulfonyl chloride(26.6 mg, 0.14 mmol) with stirring. After 3 hr, the reaction mixture is concentrated *in vacuo*. The residue is purified by column chromatography to give a tosylate. To a solution of this tosylate (94 mg, 0.91 mmol) in ether (5 mL) is added lithium diisopropylcuprate (Pr_2CuLi) (ca. 0.5 M in ether, 10 mL, excess. The resultant solution is stirred for 8 hr and then quenched with saturated aqueous solution of NH_4Cl (50 mL). Stirring is continued for an additional 2 h. The organic phase is separated and washed with NH_4Cl solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography provides 604.

C. Enone 605.

A solution of 604 (75 mg, 83 mmol) in methanol (2 mL) is treated with pyridinium p-toluenesulfonate (ca.4 mg) and stirred at 40°C for 30 min. The mixture is diluted with ether (20 mL) and washed successively with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (10 mL), and then dried over $MgSO_4$. The organic solution is concentrated *in vacuo*, and the residue is passed through a column of silica gel to

provide an alcohol. To a solution of the alcohol (62.0 mg, 68.2 mmol) in benzene (2.0 mL) is added manganese(IV) oxide (100 mg, 1.15 mmol). After stirring for 8 h at room temperature, the reaction mixture is filtered through a pad of celite. The filtrate is concentrated *in vacuo*. Flash chromatography of the residue affords α,β-unsaturated ketone 605.

D. Triol 606.

A solution of the α,β-unsaturated ketone 605 (45 mg, 56 mmol) in CH_2Cl_2 (2 mL) is cooled to 0 °C and treated with water (0.1 mL) and 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (15 mg, 66 mmol). The mixture is stirred at 0 °C for 5 hr, diluted with CH_2Cl_2 (15 mL), dried over $MgSO_4$, and filtered through a column of silica gel. Following concentration *in vacuo*, the residue is used for next step without further purification. A solution of the crude alcohol in 48% HF-acetonitrile(1:9, 1.0 mL) is stirred at room temperature for 12 hr. The reaction is quenched by saturated $NaHCO_3$ (5.0mL). The mixture is extracted with ethyl acetate(3 x 10 mL). The combined organic phase is then washed with brine (5.0 mL), dried over $MgSO_4$, concentrated *in vacuo*. The residue is purified by flash chromatography to afford 601.

EXAMPLE 57 (Figure 26)

A. Alkane 702

To a solution of iodide A (300 mg, 0.54 mmol) in ether (5 mL) is added lithium dibutylcuprate (Bu_2CuLi) (ca. 0.5 M in ether, 5.4 mL, excess) at -25°C. The resultant solution is stirred for 8 hr and then quenched with saturated aqueous NH_4Cl (50 mL). Stirring is continued for another 2 hr and the organic phase is separated. The organic solution is washed with NH_4Cl solution (20 mL) and dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography provides 702.

B. Alcohol 703.

A solution of 702 (240 mg, 0.50 mmol) in CH_2Cl_2 (6.0 mL) is cooled to -78°C. Diisobutylaluminum hydride (1.0 M in toluene, 1.50 mL, 1.50 mmol) is added dropwise over 5 min, and the resultant solution is stirred for 10 min at -78°C and 30 min at 0°C. The reaction is quenched with a saturated solution of Rochelle's salt, and the mixture is diluted with ether (60 mL), washed with Rochelle solution, and brine (30 mL each), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography provides alcohol 703.

C. Iodide 704

A solution of alcohol 703 (210 mg, 0.44 mmol) in dry benzene/ether (1:2, 5 mL) is treated with triphenylphosphine (420 mg, 1.6 mmol) and imidazole (123 mg, 1.8 mmol). After all of the imidazole dissolved, iodine (335 mg, 1.32 mmol) is added with vigorous stirring. The mixture is stirred for 2 h and then treated with triethylamine (1.8 mL). The resultant solution is diluted with CH_2Cl_2 (22 mL) and washed with saturated aqueous $Na_2S_2O_3$ (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (2 x 40 mL). The organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography to afford iodide 704.

D. Phosphonium salt 705.

The iodide 704 is mixed with triphenylphosphine (2.17 g, 8.27 mmol) and the mixture is heated at 80°C for 24 hr, cooled to room temperature, and washed with hexane (2 x 20 mL). Flash chromatography provides phosphonium salt 705.

E. Alkene 707.

A solution of 705 (260 mg, 0.30 mmol) in tetrahydrofuran (6.0 mL) is cooled to -10°C and a solution of n-butyl lithium (1.0 M in hexane, 0.29 mL, 0.29 mmol) is introduced dropwise over 5 min. The resultant solution is stirred for 50 min at room temperature and then the mixture is recooled to -78°C and aldehyde 706 (39 mg, 0.3 mmol) is

added a solution in tetrahydrofuran (1.5 mL). The mixture is stirred for 10 min at -78°C, and 1 hr at 0 °C. The reaction is quenched with saturated aqueous NH_4Cl (1.0 mL) and the resultant mixture is extracted with ether (30 mL). The ether layer is washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography to afford olefin 707 (149 mg, 85% yield).

F. Diol 708.

Acetonide 707 (147 mg, 0.25 mmol) is dissolved in 80% aqueous acetic acid (2.5 mL) at room temperature. The reaction mixture is stirred for 4 hr at room temperature and then diluted with water (20 mL). The mixture is extracted with ethyl acetate(2 x 5 mL). The combined organic layers are washed with saturated $NaHCO_3$ solution, and brine (10 mL each), and then dried over $MgSO_4$. The organic solution is concentrated *in vacuo*, and the residue is flash chromatographed over silica gel to afford diol 708.

G. Tosylate 709.

To a solution of diol 708 (134 mg, 0.25 mmol) in pyridine (2 mL) is added p-toluenesulfonyl chloride(52 mg, 0.27 mmol). After 3 hr, the reaction mixture is diluted with ether (30 mL), and washed with ice cold 1 M hydrochloric acid (60 mL), saturated $NaHCO_3$ solution (20 mL), and brine (20 mL) and then concentrated *in vacuo*. The residue is purified by column chromatography to give a monotosylate 709.

H. Epoxide 710.

A solution of tosylate 709 (145 mg, 0.21 mmol) in methanol (3.0 mL) is added potassium carbonate (10 mg) at room temperature. The mixture is stirred for 20 min, and then diluted with water (60 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers are washed with brine and concentrated *in vacuo*. Flash chromatography provides epoxide 710.

I. Alcohol 711.

To a solution of 710 (41 mg, 79 mmol) in CH_2Cl_2 (3.0 mL) at 0°C is added water (0.15 mL) and 2, 3-dichloro-5,6-dicyano-1, 4-benzoquinone (60 mg, 0.26 mmol). The mixture is stirred at 0°C for 5 hr, diluted with CH_2Cl_2 (15 mL), dried over $MgSO_4$, and filtered through a column of silica gel. Following concentration *in vacuo*, the crude 711 is used without further purification.

J. Carbamate 712.

To a solution of 711 (8.7 mg, 22 mmol) in CH_2Cl_2 (1.0 mL) is added trichloroacetyl isocyanate (0.20 mL, 1.7 mmol) at room temperature. After 30 min, the mixture is diluted with CH_2Cl_2(20 mL), and some neutral Al_2O_3 (500 mg) is added. The mixture is then stirred at room temperature for 2 hr, then filtered though a short column of silica gel, and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 712.

K. Hydroxy-urethane 701.

A solution of 712 (6.0 mg, 14 mmol) in 48% HF-acetonitrile (1:9, 1.0 mL) is stirred at room temperature for 12 hr. The reaction is quenched by saturated $NaHCO_3$ (5.0 mL). The mixture is extracted with ethyl acetate (3 x 10 mL). The combined organic phase is then washed with brine (5.0 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue is purified by flash chromatography afford 701.

EXAMPLE 58 (Figures 27 and 28)

A. Iodide 802.

A solution of alcohol 16 (*see*, Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) (410 mg, 0.360 mmol) in dry benzene/ether (1:2, 10 mL) is treated with triphenylphosphine (378 mg, 1.44 mmol) and imidazole (111 mg, 1.62 mmol). After complete dissolution of the imidazole, iodine (301 mg, 1.19 mmol) is added with vigorous stirring. The reaction mixture is stirred 2 h and then treated with triethylamine (1.7 mL). The resultant solution is diluted with CH_2Cl_2 (30 mL) and washed with saturated

aqueous $Na_2S_2O_3$ (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (2 x 40 mL). The organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography affords iodide 802.

B. Phosphonium salt 803.

To a solution of iodide 802 (410 mg, 0.325 mmol) in benzene (20 mL) is added triphenylphosphine(1.00 g, 3.81 mmol). The mixture is heated at 80°C for 24 hr, cooled to room temperature, and concentrated *in vacuo*. The residue is washed with hexane (2 x 20 mL). Flash chromatography affords phosphonium salt 803.

C. Alkene 805

A solution of 803 (460 mg, 0.30 mmol) in tetrahydrofuran (9.0 mL) is cooled to -10°C. A solution of n-butyl lithium (1.0 M in hexane, 0.29 mL, 0.29 mmol) is added dropwise over 5 min, and the resultant solution is stirred for 50 min at room temperature. Then the mixture is recooled to -78°C and a solution of aldehyde 804 (39 mg, 0.3 mmol) in tetrahydrofuran (1.5 mL) is added. The mixture is stirred for 10 min at -78°C, and 1 hr at 0 °C. The reaction is quenched with saturated aqueous NH_4Cl (20 mL), the resultant mixture is extracted with ether (40 mL), and the ether layer is washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography of the residue affords 805.

D. Diol 806

Acetonide 805 (280 mg, 0.22 mmol) is dissolved in 80% aqueous acetic acid (3.5 mL) at room temperature. The reaction mixture is stirred for 4 hr at room temperature and then diluted with water (40 mL). The mixture is extracted with ethyl acetate (2 x 10 mL). The combined organic layers are washed with saturated $NaHCO_3$ solution, and brine (10 mL each), and then dried over $MgSO_4$. The organic solution is concentrated *in vacuo*, and the residue is flash chromatographed over silica gel to afford diol 806.

E. Tosylate 807.

To a solution of diol 806 (235 mg, 0.19 mmol) in pyridine (2 mL) at 0 °C is added p-toluenesulfonyl chloride (45 mg, 0.23 mmol). After 3 hr, the reaction mixture is diluted with ether (30 mL), and washed with ice cold 1 M hydrochloric acid (30 mL), saturated $NaHCO_3$ solution (20 mL), and brine (20 mL) and then concentrated *in vacuo*. The residue is purified by column chromatography to give a monotosylate 807.

F. Epoxide 808.

To a solution of tosylate 807 (187 mg, 0.21 mmol) in methanol (3.0 mL) is added potassium carbonate (10 mg) at room temperature. The mixture is stirred for 20 min, and then diluted with water (60 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine and concentrated *in vacuo*. Flash chromatography provides epoxide 808.

G. Lactone 809.

To a solution of 808 (110 mg, 93 mmol) in tetrahydrofuran-acetonitrile (10 mL, 2:1) is added a phosphate buffer solution (pH = 7.0, 3.5 mL), and $HgCl_2$ (2.3 g). The suspension is stirred at room temperature for 40 min, then diluted with ether (30 mL), washed with brine(2 x 30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography affords the lactol as an α/β anomeric mixture. This material is used directly in the next oxidation: Under argon atmosphere, a solution of the lactols in dimethylsulfoxide (3.0 mL) is treated with acetic anhydride (0.60 mL). After 2 days at room temperature, the mixture is diluted with ether (50 mL), washed with saturated $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography provides 809.

H. Alcohol 810.

To a solution of 809 (90 mg, 79 mmol) in CH_2Cl_2 (3.0 mL) at 0°C is added water (0.15 mL) and 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone(60 mg, 0.26 mmol). The mixture is stirred at 0°C for 5 hr, diluted with CH_2Cl_2 (15 mL),

dried over $MgSO_4$, and filtered through a column of silica gel. Following concentration *in vacuo*, the crude 810 is used in the next reaction without further purification.

I. Carbamate 811

To a solution of 810 (22 mg, 22 mmol) in CH_2Cl_2 (1.0 mL) is added trichloroacetyl isocyanate (0.20 mL, 1.7 mmol) at room temperature. After 30 min, the mixture is diluted with CH_2Cl_2(20 mL), and some neutral Al_2O_3 (500 mg) is added. The mixture is then stirred at room temperature for 2hr, then filtered though a short column of silica gel, and concentrated *in vacuo*. Flash chromatography affords 811.

J. Epoxide analog 812.

A solution of 811 (15 mg, 14 mmol) in tetrahydrofuran(1.0 mL) is cooled to 0°C, and treated with a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran(0.14 mL, 0.14 mmol). The reaction mixture is stirred for 2 hr, and diluted with water (20 mL). The mixture is extracted with ethyl acetate (3 x 10 mL). The combined organic phase is then washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo*. Flash chromatography affords 801.

EXAMPLE 59 (Figure 29)

A. Alcohol 903.

Phosphonium salt 15 (98.0 mg, 0.092 mmol) is dried azeotropically with dry benzene and heated at 50°C under vacuum for 3 hr before use. It is then dissolved in tetrahydrofuran (0.7 mL). Sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 86 mL, 0.0855 mmol) is added at -78°C, and the mixture is stirred for 20 min and then recooled to -78°C. A solution of aldehyde 902 (60 mmol) in tetrahydrofuran (300 mL) is added, and the mixture is stirred for 10 min at -78°C, and 2 hr at room temperature. The reaction is quenched with saturated aqueous NH_4Cl (1.0 mL). The resultant mixture is extracted with ether (30 mL), and the ether layer is washed with water (30 mL) and brine

(30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography provides an olefin. A solution of the olefin (44 mmol) in CH_2Cl_2 is cooled to -78°C. Diisobutylaluminum hydride (1.0 M in toluene, 440 mL, 0.40 mmol) is added dropwise over 5 min, and the resultant solution is stirred for 10 min at -78 °C and 30 min at 0 °C. The reaction is quenched with a saturated solution of Rochelle's salt, and the mixture is diluted with ether (60 mL), washed with Rochelle solution, and brine (30 mL each), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography provides alcohol 903.

B. Diene 905.

A solution of 903 (0.012 mmol) and Et_3N (42 mL, 0.30 mmol) in CH_2Cl_2 (2.0 mL) is cooled to 0°C and a solution of SO_3-pyridine complex (40 mg, 0.251 mmol) in dimethylsulfoxide (0.6 mL) is added. The mixture is stirred at 0°C for 45 min and then diluted with ethyl acetate (30 mL), washed with aqueous $NaHSO_4$ (1.0 M, 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography affords an aldehyde. A solution of allyldiphenylphosphine 904 (0.19 mmol) in tetrahydrofuran (1.0 mL) is cooled to -78°C and t-butyl lithium (1.7 M in pentane, 0.122 mmol) is added. The mixture is stirred at 0°C for 30 min, recooled to -78°C and treated titanium tetra-*I*-propoxide (0.15 mmol). After 30 min, a cold (-78°C) solution of the aldehyde (0.26 mmol) in tetrahydrofuran (1.0 mL) is introduced via cannula, and the mixture is stirred 10 min further at -78°C and at 0°C for 1 hr. Iodomethane (0.32 mmol) is added, and the reaction is maintained at 0°C for 30 min, warmed to room temperature, protected from light, and stirred overnight. The reaction mixture is diluted with ether (30 mL), washed with 1.0 M aqueous $NaHSO_4$ and brine (30 mL each), dried over $MgSO_4$, concentrated *in vacuo*. Flash chromatography affords diene 905.

C. Glycoside 908.

A solution of 905 (83 mmol) in methanol (2 mL) is

treated with pyridinium p-toluenesulfonate (ca.4 mg) and stirred at 40°C for 30 min. The mixture is diluted with ether (20 mL) and washed successively with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (10 mL), and then dried over $MgSO_4$. The organic solution is concentrated *in vacuo*, and the residue is passed through a column of silica gel to give an alcohol.

To a solution of glycosyl bromide 906 (75 mmol) in CH_2Cl_2(2.0 mL) is added $HgBr_2$ (7 mmol) and powdered molecular sieves (4Å, 50 mg) and stirred for 60 min at room temperature. The mixture is then cooled to 0°C, and the alcohol (74 mmol) prepared above is added in CH_2Cl_2 (0.7 mL). The resultant mixture is stirred 6 hr at 0°C and then warmed to room temperature and diluted with CH_2Cl_2 (10 mL), and filtered through a pad of celite. The filtrate is washed with aqueous KI solution, and dried over $MgSO_4$. The organic solution is concentrated *in vacuo*, and the residue is passed through a column of silica gel to give an anomeric mixture of glycosides 908.

D. Triol 901.

To a solution of 908 (79 mmol) in CH_2Cl_2 (3.0 mL) at 0°C is added water (0.15 mL) and 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (60 mg, 0.26 mmol). The mixture is stirred at 0°C for 5 hr, diluted with CH_2Cl_2 (15 mL), dried over $MgSO_4$, and filtered through a column of silica gel. Following concentration *in vacuo*, the crude alcohol is used for next step without further purification. To a solution of the alcohol (22 mmol) in CH_2Cl_2 (1.0 mL) is added trichloroacetyl isocyanate (0.20 mL, 1.7 mmol) at room temperature. After 30 min, the mixture is diluted with CH_2Cl_2(20 mL), and some neutral Al_2O_3 (500 mg) is added. The mixture is then stirred at room temperature for 2 hr, then filtered though a short column of silica gel, and concentrated *in vacuo*. Flash chromatography affords a carbamate. A solution of the carbamate (14 mmol) in 48% HF-acetonitrile (1:9, 1.0 mL) is stirred at room temperature

for 12 hr. The reaction is quenched by saturated $NaHCO_3$ (5.0 mL). The mixture is extracted with ethyl acetate (3 x 10 mL). The combined organic phase is then washed with brine(5.0 mL), dried over $MgSO_4$, concentrated *in vacuo*. Flash chromatography affords 901.

EXAMPLE 60 (Figure 30)

A. Olefin 1001

A solution of model phosphonium salt (0.0917 mmol) in THF (700 mL) is cooled to -78 °C and treated with NaHMDS (1.0 M in THF, 85.5 mL, 0.0855 mmol). The mixture is stirred for 20 min at 0 °C, recooled to -78 °C and aldehyde C (0.0570 mmol) in THF (300 mL) is added. After 10 min at -78 °C and 2 h at room temperature, the mixture is quenched with saturated aqueous NH_4Cl (1.0 mL) and extracted with ether (30 mL). The ether solution is washed with water, brine (30 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography provides olefin 1001.

B. Lactone 1002

A solution of olefin 1001 (0.00597 mmol) in THF/CH_3CN (2:1, 1.50 mL) is treated with pH 7.0 phosphate buffer (500 mL) and $HgCl_2$ (215 mg). The suspension is stirred at room temperature for 40 min, diluted with ether (30 mL), washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (5% ethyl acetate/hexane) provides a mixture of lactols as a colorless oil which is further treated with DMSO (1.0 mL) and Ac_2O (200 mL) at room temperature for 2 days. The mixture is diluted with ether (30 mL), washed with saturated $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography provides lactone 1002.

C. Model Compound 1003

A solution of olefin 1002 (5.5 mmol) in 48% HF-CH_3CN (1:9, 1.0 mL) is stirred at room temperature for 12 h, then quenched with saturated aqueous $NaHCO_3$ (5.0 mL). The mixture is extracted with ethyl acetate (3 x 10 mL). The combined organic extracts are washed with brine (5.0 mL),

dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (gradient elution, 1:30 to 1:6 MeOH/CHCl3) provides 1003.

EXAMPLE 61 (Figures 31 and 32)

I. General procedure for synthesis of hydroxy aldehydes 1104.

A. TBS ether 1102a

A solution of bromide 1101a (*see*, Jacquesy, *et al.*, *Tetrahedron* **1981**, *37*, 747) (20 mmol) in ether (40 mL) is added slowly to a -78 °C solution of tert-butyllitium (40 mmol, 1.7 M in pentane). After 1 h at -78 °C, the cold solution is transferred to a suspension of copper (I) iodide (10 mmol) in ether at 0 °C. After an additional 30 min at 0 °C, a solution of benzyl (S)-(+)-glycidyl ether (9 mmol) in ether (20 mL) is added and the reaction is allowed to warm to room temperature. After 18-24 h, the reaction is quenched by the addition of tert-butyldimethylsilyl triflate (10 mmol). The reaction mixture is poured into saturated aqueous sodium bicarbonate (100 mL). The aqueous layer is separated and extracted with ether (2 x 50 mL). The combined organics are washed with saturated aqueous brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 1102a.

B. Alcohol 1103a.

To a solution of 1102a (6 mmol) in ethyl acetate-ethanol (8:1, 90 mL) is added palladium on carbon (10% wet, 500 mg). The mixture is stirred under hydrogen atmosphere for 3-6 h, then filtered and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 1103a.

C. Aldehyde 1104a.

Oxalyl chloride (1.5 mmol) is added dropwise to a -78 °C solution of dimethyl sulfoxide (3 mmol) in

dichloromethane (4 mL). After 15 min, a -78 °C solution of 1103a (1 mmol) in dichloromethane (2 mL) is added via canula. After an additional 15 min, diisopropylethylamine (4.5 mmol) is added and the reaction is gradually warmed to room temperature over 1 h and quenched with aqueous sodium bisulfate. The mixture is diluted with ether (50 mL) and is washed with water (2 x 30 mL), saturated aqueous brine (2 x 30 mL), is dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 1104a.

II. General procedure for the conversion of 1104 to arene analog 1111:

A. Diene 1105.

Phosphonium salt 15 (*see*, Smith, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 12011) (0.2 mmol) is dissolved in anhydrous tetrahydrofuran (2 mL) and chilled to 0 °C. A solution of sodium bis(trimethylsilyl)amide (0.2 mmol, 1.0 M in tetrahydrofuran) is added and the reaction mixture is stirred 30 min at 0 °C. After cooling to -78 °C, a solution of aldehyde 1104 (0.1 mmol) in tetrahydrofuran (2 mL) is added and the mixture is stirred 10 min at -78 °C and 2 h at room temperature. Saturated aqueous ammonium chloride (2 mL) is added and the resultant mixture is extracted with ether (3 x 20 mL). The ethereal layer is washed with water (2 x 25 mL) and saturated aqueous brine (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 1105.

B. Hydroxy diene 1106.

A -78 °C solution of 1105 (0.05 mmol) in CH_2Cl_2 (5 mL) is treated with diisobutylaluminum hydride (0.5 mL, 1.0 M in toluene). The resultant solution is stirred 10 min at -78 °C and 30 min at 0 °C. The reaction is quenched with a saturated solution of sodium potassium tartrate (50 mL) and the mixture is diluted with ether (60 mL). The organic layer is separated, dried over magnesium sulfate, and concentrated *in vacuo*. The residue is purified by flash

chromatography to afford 1106.

C. Aldehyde 1107.

Oxalyl chloride (1.5 mmol) is added dropwise to a -78 °C solution of dimethyl sulfoxide (3 mmol) in dichloromethane (4 mL). After 15 min, a -78 °C solution of 1106 (1 mmol) in dichloromethane (2 mL) is added via canula. After an additional 15 min, diisopropylethylamine (4.5 mmol) is added and the reaction is gradually warmed to room temperature over 1 h and quenched with aqueous sodium bisulfate. The mixture is diluted with ether (50 mL) and is washed with water (2 x 30 mL), saturated aqueous brine (2 x 30 mL), is dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 1107.

D. Tetraene 1108.

A solution of diphenylallylphosphine (0.08 mL, 0.38 mmol) in tetrahydrofuran (2 mL) is cooled to -78 °C and tert-butyllithium (0.14 mL, 1.7 M in pentane) is added. The mixture is warmed to 0 °C for 30 min, then recooled to -78 °C and treated with titanium (IV) isopropoxide (0.30 mmol). After 30 min, aldehyde 1107 (0.30 mmol) is introduced as a solution in tetrahydrofuran (2 mL). The resultant solution is stirred at -78 °C for 15 min and at 0 °C for 1 h. Methyl iodide (0.64 mmol) is added, and the reaction is warmed to room temperature for 12 h. The reaction mixture is diluted with ether (60 mL), washed with aqueous sodium bisulfate (30 mL, 1.0 M), saturated aqueous brine (30 mL), and is dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 1108.

E. Alcohol 1109.

To a solution of 1108 (0.050 mmol) in dichloromethane (3 mL) at 0 °C is added water (50 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.018 mmol). After 1 h, the reaction mixture is diluted with ethyl acetate (50 mL), washed with saturated aqueous brine (3 x 25 mL), dried over magnesium sulfate and concentrated *in vacuo*.

The residue is purified by flash chromatography to afford 1109.

F. Carbamate 1110.

To a solution of 1109 (0.010 mmol) in dichloromethane (2 mL) is added trichloroacetyl isocyanate (1.00 mmol). After 30 min, the reaction mixture is diluted with dichloromethane (4 mL) and neutral alumina (1 g) is added. The resultant suspension is stirred an additional 4 h. The reaction mixture is filtered and the concentrated filtrate is chromatographed on silica gel to afford 1110.

G. Arene analog 1111.

A solution of 1110 (0.010 mmol) in 48% hydrofluoric acid-acetonitrile (1:9, 2 mL) is stirred at ambient temperature. After 12 h, saturated aqueous sodium bicarbonate (25 mL) is added and the mixture is extracted with ethyl acetate (3 x 20 mL). The combined organics are dried over magnesium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography to afford 1111.

Example 62

Synthesis of Aldehyde 67

Enone (64). To a -78 °C solution of aldehyde **27** (1.94 g, 6.13 mmol prepared from commercially available methyl *(S)*-(+)-3-hydroxy-2-methyl propionate generally according to Smith, et. al., *J. Am. Chem. Soc.* **1995**, *117*, 12011) in CH_2Cl_2 (50 mL) was added (dropwise over 3 min) a -78 °C solution of $TiCl_4$ (0.68 mL, 6.18 mmol) in CH_2Cl_2 (6 mL). The resultant solution was stirred an additional 3 min at -78 °C. 4-Methyl-2-trimethylsiloxy- 1,3-pentadiene (1.89 g, 11.1 mmol, *see* Paterson, *Tetrahedron Lett.* **1979**, 1519) was added dropwise over 2 min and the reaction mixture was further stirred at -78 °C for 2 h. A solution comprised of pH 8 phosphate buffer (100 mL) and saturated aqueous bicarbonate (50 mL) was added and the biphasic solution was warmed to ambient temperature, diluted with water (100 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The combined

extracts were washed with saturated brine (75 mL), dried ($MgSO_4$) and concentrated. The residual oil was diluted with CH_2Cl_2/hexanes (1:1, 30 mL), cooled to 0 °C and treated with trichloroacetic acid (1.54 g, 9.42 mmol). After 5 h, the reaction mixture was diluted with hexanes (75 mL) and washed with water (2 x 50 mL), pH 8 phosphate buffer (50 mL) and saturated brine (50 mL) and was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (hexanes/CH_2Cl_2/ethyl acetate, 12:4:1) afforded **64** (1.21 g, 56 %) as a colorless oil: $[\alpha]_D^{23}$ -10.6° © 0.88, $CHCl_3$); ^{1}H NMR (500 MHZ, $CDCl_3$) d 6.09 (m, 1 H), 4.78 (ddd, J = 10.0, 6.6, 4.3 Hz, 1 H), 3.65 (t, J = 2.8 Hz, 1 H), 2.72 (dd, J = 15.8, 4.3 Hz, 1 H), 2.66 (dd, J = 15.8, 6.7 Hz, 1 H), 2.62 (qd, J = 7.6, 3.2 Hz, 1 H), 2.13 (d, J = 1.1 Hz, 3 H), 2.07 (dqd, J = 10.0, 6.8, 2.4 Hz, 1 H), 1.87 (d, J = 1.2 Hz, 3 H), 1.25 (d, J = 7.6 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 196.9, 173.6, 156.8, 124.1, 77.8, 74.3, 47.0, 43.9, 33.6, 27.7, 25.7, 20.9, 18.0, 16.1, 13.8, -4.5, -4.7.

Alcohol (65). A solution of enone **64** (109 mg, 0.307 mmol) in toluene (8 mL) was cooled to -95 °C and treated with K-Selectride' (1.0 M in THF, 0.35 mL). After 2 h, glacial acetic acid (0.015 mL) was added and the resultant solution was warmed to ambient temperature and treated with pH 7 aqueous phosphate buffer solution (10 mL) and 30% aqueous hydrogen peroxide (0.5 mL). After 2 h, the aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL) and the combined organics were dried ($MgSO_4$) and concentrated. Flash chromatography (15% ethyl acetate/hexanes) afforded **65** (70 mg, 64%) as a colorless oil: ^{1}H NMR (500 MHZ, $CDCl_3$) d 5.21 (apparent dt, J = 8.6, 1.3 Hz, 1 H), 4.75 (br t, J = 9.1 Hz, 1 H), 4.60 (td, J = 9.9, 2.3 Hz, 1 H), 3.67 (t, J = 3.0 Hz, 1 H), 2.66 (qd, J = 7.5, 3.4 Hz, 1 H), 1.90 (dqd, 9.7, 6.8, 2.6 Hz, 1 H), 1.83 (ddd, J = 14.5, 9.9, 2.4 Hz, 1 H), 1.71 (d, J = 1.1 Hz, 3 H), 1.70 (d, J = 1.2 Hz, 3 H), 1.65 (br s,

1 H), 1.60 (ddd, J = 14.5, 10.1, 2.9 Hz, 1 H), 1.26 (d, J = 7.6 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H),0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 174.0, 134.8, 127.7, 77.8, 74.2, 64.1, 43.7, 41.5, 34.6, 25.7, 25.6, 18.2, 17.9, 16.0, 13.7, -4.6, -4.8.

Silyl Ether (66). A solution of alcohol **65** (493 mg, 1.38 mmol) and imidazole (306 mg, 4.49 mmol) in DMF (6 mL) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl chloride (386 mg, 2.56 mmol). The resultant solution was stirred 12 h at ambient temperature, diluted with ether (75 mL), washed with water (2 x 15 mL) and saturated brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (5% ethyl acetate/hexanes) afforded **66** (615 mg, 95%) as a colorless oil: ^1H NMR (500 MHZ, $CDCl_3$) d 5.11 (apparent dt, J = 8.6, 1.3 Hz, 1 H), 4.71 (ddd, 10.4, 8.7, 2.2 Hz, 1 H), 5.55 (td, J = 10.4, 1.7 Hz, 1 H), 3.65 (t, J = 2.7 Hz, 1 H), 2.63 (qd, J = 7.6, 3.0 Hz, 1 H), 1.83 (dqd, 10.0, 6.8, 2.5 Hz, 1 H), 1.74 (ddd, J = 14.2, 10.5, 1.8 Hz, 1 H), 1.68 (d, J = 1.1 Hz, 3 H), 1.65 (d, J = 1.2 Hz, 3 H), 1.44 (ddd, J = 14.2, 10.6, 2.3 Hz, 1 H), 1.26 (d, J = 7.6 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H);

Aldehyde (67). A solution of olefin **66** (615 mg, 1.30 mmol) in CH_2Cl_2 (20 mL) was cooled to -78 °C and treated with a stream of ozone and oxygen until the colorless solution became steel-blue in appearance. The reaction mixture was purged with a stream of air for 10 min, followed by the cautious addition of triphenylphosphine (375 mg, 1.42 mmol). The cooling bath was removed and the solution was stirred at ambient temperature for 1 h, concentrated, and chromatographed (20% ethyl acetate/hexanes) to afford **67** (486 mg, 84%) as a colorless oil that solidified upon standing at 0 °C. ^1H NMR (500 MHZ, $CDCl_3$) d 9.67 (br s, 1 H), 4.52 (td, J = 10.5, 2.1 Hz, 1 H), 4.46 (dd, J = 10.5, 3.5 Hz, 1 H), 3.67 (t, J = 2.3 Hz, 1 H), 2.66 (qd, J = 7.6,

2.6 Hz, 1 H), 1.95-1.84 (m, 3 H), 1.77 (ddd, J = 14.1, 10.5, 2.1 Hz, 1 H), 1.27 (d, J = 7.6 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 203.2, 173.1, 76.0, 74.7, 73.7, 44.2, 36.2, 34.1, 25.72, 25.66, 18.1, 17.9, 16.5, 14.0, -4.55, -4.63, -4.9, -5.2.

Example 63

Synthesis of Phosphonium Salt (49) Employing Ultrahigh Pressure.

Iodine (132 mg, 0.52 mmol) was added in one portion to a vigorously stirred solution of alcohol **40** (122 mg, 0.176 mmol, prepared from commercially available methyl *(S)*-(+)-3-hydroxy-2-methyl propionate generally according to Smith, et. al., *J. Am. Chem. Soc.* **1995**, *117*, 12011), PPh_3 (172 mg, 0.656 mmol) and imidazole (42 mg, 0.62 mmol) in benzene/ether (1:2, 1.5 mL) at 0 °C. The resultant solution was stirred 1 h at 0 °C and 1 h at ambient temperature. The mixture was diluted with ether (10 mL), washed with saturated aqueous sodium metabisulfite (5 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography afforded a colorless oil (147 mg, 100 % yield). This material was combined with diisopropylethylamine (0.016 mL, 0.091 mmol), triphenylphosphine (152 mg, 0.58 mmol) and benzene/toluene (7:3, 1.0 mL) in a plastic syringe and subjected to a pressure of 12.8 Kbar. After 6 days, the reaction mixture was concentrated and chromatographed (10% $MeCN/CHCl_3$) to provide **49** [138 mg, 74% yield from **40**] as a pale yellow foam: ^1H NMR (500 MHZ, $CDCl_3$; concentration-dependent) d 7.82-7.76 (m, 15 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 5.35 (s, 1 H), 5.30 (d, *J* = 10.5 Hz, 1 H), 4.07 (dd, *J* = 11.2, 4.7 Hz, 1 H), 3.77 (s, 3 H), 3.73-3.67 (m, 2 H), 3.56 (dd, *J* = 7.0, 1.8 Hz, 1 H), 3.48 (dd, *J* =

9.8, 1.7 Hz, 1 H), 3.46 (apparent t, J = 11.1 Hz, 1 H), 3.31 (ddd, J = 15.6, 11.2, 11.2 Hz, 1 H), 2.49 (ddq, J = 10.5, 6.4, 6.4 Hz, 1 H), 2.25 (apparent t, J = 12.1 Hz, 1 H), 2.10-1.92 (m, 3 H), 1.85 (dqd, J = 7.1, 7.1, 1.8 Hz, 1 H), 1.57-1.52 (m, 1 H), 1.56 (s, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.852 (s, 9 H), 0.849 (s, 9 H), 0.72-0.71 (m, 3 H), 0.71 (d, J = 6.6 Hz, 3 H), 0.69 (d, J = 6.9 Hz, 3 H), 0.10 (s, 3 H), -0.02 (s, 3 H), -0.03 (s, 3 H), -0.07 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.8, 135.2 (d, J_{CP} = 2.6 Hz), 133.5 (d, J_{CP} = 10.0 Hz), 132.9, 131.4, 130.6 (d, J_{CP} = 12.6 Hz), 130.3, 127.3, 118.4 (d, J_{CP} = 85.5 Hz), 113.4, 101.0, 83.2, 80.1 (d, J_{CP} = 14.0 Hz), 78.3, 73.2, 55.3, 38.1, 37.4, 36.0, 33.7 (d, J_{CP} = 4.4 Hz), 33.6, 30.7, 26.1, 25.5 (d, J_{CP} = 49.7 Hz), 22.9, 18.33, 18.29, 17.2, 17.1, 12.5, 12.1, 10.9, -3.2, -3.6, -3.7, -4.0; high resolution mass spectrum (FAB, NBA) *m/z* 937.5708 [$(M-I)^+$; calcd for $C_{57}H_{86}O_5PSi_2$: 937.5751].

Example 64

Synthesis of Diene (76)

Phosphonium salt **49** (166 mg, 0.156 mmol), was heated to 50 °C under vacuum (0.1 torr) for 18 h, dissolved in 0.8 mL of toluene, and cooled to 0 °C. The resultant solution was treated with potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.32 mL), was stirred 20 min at 0 °C and 20 min at ambient temperature and re-chilled to -78 °C. To this reaction mixture was transferred via cannula a solution of aldehyde **67** (58 mg, 0.13 mmol) in toluene (0.3 mL + 2 x 0.2 mL rinse). The resultant solution was allowed to slowly warm to -20 °C during 1 h. A solution of pH 7 phosphate buffer was added and the biphasic solution was warmed to ambient temperature and extracted with CH_2Cl_2 (4 x 20 mL). The combined organics were dried ($MgSO_4$), concentrated, and chromatographed (10% ethyl acetate/hexanes) to afford **76** (83

mg, 57%) as a colorless oil that solidified upon standing: $[\alpha]_D^{23}$ +32.1° © 0.68, $CHCl_3$); ^1H NMR (500 MHZ, $CDCl_3$) d 6.97 (br d, J = 8.7 Hz, 2 H), 6.87 (br d, J = 8.7 Hz, 2 H), 5.34 (s, 1 H), 5.29 (dd, J = 11.1, 7.8 Hz, 1 H), 5.19 (t, J = 10.6 Hz, 1 H), 5.07 (d, J = 10.0 Hz, 1 H), 4.78 (br t, J = 9.1 Hz, 1 H), 4.52 (br t, J = 10.0 Hz, 1 H), 4.10 (dd, J = 11.1, 4.6 Hz, 1 H), 3.80 (s, 3 H), 3.64 (m, 2 H), 3.54-3.46 (m, 2 H), 3.25 (t, J = 5.3 Hz, 1 H), 2.65-2.57 (m, 2 H), 2.51 (m, 1 H), 2.31 (t, J = 12.2 Hz, 1 H), 2.06 (m, 1 H), 1.96 (m, 1 H), 1.90 (dqd, J = 7.1, 7.0, 1.5 Hz, 1 H), 1.78 (ddd, J = 10.3, 6.6, 2.1 Hz, 1 H), 1.72 (ddd, J = 14.0, 11.0, 1.5 Hz, 1 H), 1.67 (br d, J = 11.6 Hz, 1 H), 1.56 (m, 1 H), 1.55 (s, 3 H), 1.20 (d, J = 7.6 Hz, 3 H), 1.02 (d, J = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.75 (d, J = 6.9 Hz, 3 H), 0.74 (d, J = 6.7 Hz, 3 H), 0.073 (s, 3 H), 0.071 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 6 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.2, 159.8, 133.6, 132.4, 131.9, 131.5, 131.4, 127.3, 113.4, 101.0, 83.4, 80.4, 78.4, 76.9, 74.9, 73.3, 64.7, 55.2, 44.1, 42.7, 38.0, 37.4, 35.2, 34.2, 34.0, 30.8, 26.3, 26.2, 25.9, 25.7, 23.2, 18.43, 18.39, 18.1, 17.9, 17.1, 16.4, 16.2, 14.0, 12.8, 12.1, 10.8, -2.9, -3.5, -3.8, -4.37, -4.41, -4.5, -4.87, -4.88.
Recrystallization from hexanes afforded fine needles: mp 117-119 °C.

Example 65

Synthesis of Aldehyde (77).

A solution of acetal **76** (20 mg, 0.018 mmol) in CH_2Cl_2 (2 mL) was cooled to -78 °C and diisobutylaluminum hydride (1.0 M in toluene, 0.18 mL, 0.18 mmol) was added over 5 min. After an additional 10 min at -78 °C and 30 min at 0 °C, the reaction was quenched with saturated aqueous potassium sodium tartrate (0.5 mL). The mixture was then diluted with ether (20 mL), washed with saturated aqueous

potassium sodium tartrate and brine (10 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate/hexanes) provided an epimeric mixture of hydroxy-lactols (14.7 mg, 74% yield) as a colorless oil. The mixture of lactols (14.7 mg, 0.0133 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C and treated with pyridinium dichromate (26 mg, 0.069 mmol). The reaction mixture was stirred 12 h at ambient temperature, diluted with ethyl acetate (10 mL), filtered (Celite) and concentrated. Flash chromatography (10% ethyl acetate/hexanes) afforded **77** (12.4 mg, 62% from **76**) as a colorless oil: ^{1}H NMR (500 MHZ, $CDCl_3$) d 9.80 (d, J = 2.4 Hz, 1 H), 7.22 (br d, J = 8.6 Hz, 2 H), 6.86 (br d, J = 8.6 Hz, 2 H), 5.30 (dd, J = 11.1, 7.9 Hz, 1 H), 5.20 (dd, J = 10.9, 10.1 Hz, 1 H), 5.11 (d, J = 10.0 Hz, 1 H), 4.79 (apparent t, J = 9.2 Hz, 1 H), 4.52 (br t, J = 9.6 Hz, 1 H), 4.47 (s, 2 H), 3.80 (s, 3 H), 3.62 (t, J = 2.5 Hz, 1 H), 3.59 (m, 2 H), 3.26 (t, J = 5.3 Hz, 1 H), 2.75 (m, 1 H), 2.62 (m, 2 H), 2.50 (m, 1 H), 2.24 (t, J = 12.4 Hz, 1 H), 1.99-1.88 (m, 2 H), 1.83-1.65 (m, 3 H), 1.59 (s, 3 H), 1.58 (m, 1 H), 1.21 (d, J = 7.6 Hz, 3 H), 1.13 (d, J = 7.0 Hz, 3 H), 1.04 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.94 (s, 9H), 0.91 (s, 9 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.75 (d, J = 6.8 Hz, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 6 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 204.5, 173.2, 159.3, 133.5, 132.5, 132.3, 130.8, 130.3, 129.1, 113.8, 82.6, 80.4, 76.9, 74.9, 74.4, 64.6, 55.3, 49.5, 44.1, 42.7, 40.3, 37.4, 36.8, 35.2, 35.0, 34.2, 26.3, 26.2, 25.9, 25.7, 23.1, 18.5, 18.4, 18.1, 17.9, 17.1, 16.4, 16.2, 14.1, 13.4, 12.2, 11.4, -3.0, -3.3, -3.4, -4.3, -4.4, -4.5, -4.9.

Example 66

Synthesis of Tetraene (58)

Method A. A solution of allyldiphenylphosphine (0.0035 mL, 0.0162 mmol) in anhydrous THF was cooled to -78

°C and *t*-BuLi (1.7 M in pentane, 0.010 mL, 0.017 mmol) was added. The mixture was stirred at 0 °C for 30 min, recooled to -78 °C and treated $Ti(OiPr)_4$ (0.005 mL, 0.017 mmol). After 30 min, a cold (-78 °C) solution of the aldehyde **77** (3.5 mg, 0.0032 mmol) in THF (0.25 mL + 0.25 mL rinse) was introduced via cannula, and the mixture was stirred 10 min further at -78 °C and at 0 °C for 30 min. Methyl Iodide (0.0025 mL, 0.04 mmol) was then added, and the reaction was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ether (10 mL), washed with 1.0 M aqueous $NaHSO_4$ and brine (5 mL each), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (2% ethyl acetate/hexane) gave a 1.2:1 mixture of Z/E isomers (2.1 mg, 58%) as an oil. Pipette flash chromatography on 10% silver nitrate-silica gel (5% ether/hexanes) furnished the Z-olefin **58** as a colorless oil: ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.25 (d, J = 8.2 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.57 (dddd, J = 16.8, 11.0, 11.0, 0.7 Hz, 1 H), 6.00 (apparent t, J = 11.1 Hz, 1 H), 5.55 (apparent t, J = 10.5 Hz, 1 H), 5.26 (dd, J = 11.2, 7.8 Hz, 1 H), 5.20-5.16 (m, 2 H), 5.09 (d, J = 10.1 Hz, 1 H), 5.05 (d, J = 2.2 Hz, 1 H), 5.03 (d, J = 10.0 Hz, 1 H), 4.67 (apparent t, J = 9.1 Hz, 1 H), 4.49 (AB_q, J_{AB} = 10.6 Hz, $\Delta\gamma_{AB}$ = 41.3 Hz, 2 H), 3.78 (s, 3 H), 3.68 (apparent t, J = 10.2 Hz, 1 H), 3.52 (apparent t, J = 2.6 Hz, 1 H), 3.43 (dd, J = 4.8, 3.9 Hz, 1 H), 3.24-3.21 (m, 2 H), 3.01-2.94 (m, 1 H), 2.67 (dq, J = 12.8, 7.4 Hz, 1 H), 2.61 (dq, J = 12.8, 7.5 Hz, 1 H), 2.71-2.57 (m, 1 H), 2.46-2.39 (m, 1 H), 2.00 (apparent t, J = 12.4 Hz, 1 H), 1.83-1.73 (m, 3 H), 1.64 (br d, J = 14.0 Hz, 1 H), 1.62-1.52 (m, 2 H), 1.55 (d, J = 0.5 Hz, 3 H), 1.36 (ddd, J = 13.7, 10.8, 1.5 Hz, 1 H), 1.26 (d, J = 7.4 Hz, 3 H), 1.25 (d, J = 7.4 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 7.1 Hz, 3 H),

0.93 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.89-0.86 (m, 3 H), 0.86 (s, 9 H), 0.73 (d, J = 6.8 Hz, 3 H), 0.70 (d, J = 6.7 Hz, 3 H), 0.08 (s, 6 H), 0.05 (s, 3 H), 0.02 (s, 3 H), 0.013 (s, 3 H), 0.010 (s, 6 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.1, 134.5, 134.3, 132.2, 131.9, 131.8, 131.2, 129.13, 129.07, 117.6, 113.7, 84.6, 80.9, 80.5, 76.5, 75.0, 74.2, 65.5, 55.3, 42.5, 41.9, 40.2, 37.2, 36.1, 35.4, 35.3, 34.5, 29.7, 26.3, 26.0, 25.9, 25.1, 23.1, 18.7, 18.6, 18.5, 18.14, 18.09, 17.0, 16.8, 15.6, 14.8, 14.4, 11.6, 10.6, -2.8, -3.2, -3.3, -3.6, -4.2, -4.5, -4.90, -4.93; high resolution mass spectrum (FAB, NBA) *m/z* 1195.8001 [$(M+Na)^+$; calcd for $C_{66}H_{124}O_7SSi_4Na$: 1195.8042].

Method B. A vigorously stirred suspension of chromium(III) chloride (7.8 mg, 0.048 mmol) in anhydrous THF (0.6 mL) was cooled to 0 °C and treated with lithium aluminum hydride (1.0 M in ether, 0.022 mL, 0.022 mmol). The resultant solution was stirred 20 min at room temperature and re-cooled to 0 °C. Aldehyde **77** (3.9 mg, 0.035 mmol) was added in THF (0.4 mL). After 10 min, a mixture of 3-bromo-1-trimethylsilyl-1-propene and 3-bromo-3-trimethlsilyl-1-propene (3:1, 0.002 mL, 0.01 mmol, *see*, Hodgson, *et*. al., *Tetrahedron Lett.* **1992**, *33*, 4761) was added. The reaction mixture was stirred at ambient temperature for 12 h and then diluted with hexanes-ethyl acetate (9:1), washed with water, saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated. Flash chromatography afforded a 2.8:1 mixture of hydroxy silanes (3.8 mg, 89%). The mixture was dissolved in THF (0.6 mL), cooled to 0 °C and treated with potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.068 mL, 0.34 mmol). After 15 min, trichloroacetic acid (5 mg, 0.03 mmol) was added and the reaction mixture was diluted with hexanes and washed with water and brine. The combined aqueous washings were further extracted with hexanes. The combine organics were dried over $MgSO_4$ and concentrated in vacuo. Flash Chromatography afforded (2.6 mg, 65% yield for 2

steps) of tetraene **58** as a colorless oil.

Method C. Phosphonium salt **75** (120 mg, 0.11 mmol) was heated to 50 °C under vacuum (0.1 torr) for 18 h and dissolved in 0.4 mL of anhydrous toluene. The resultant solution was cooled to 0 °C and was treated with potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.23 mL, 0.115 mmol). The resultant solution was stirred 20 min at 0 °C and 20 min at ambient temperature before being chilled to -78 °C. Aldehyde **67**(46 mg, 0.10 mmol) was added in toluene (0.4 mL) and the reaction mixture was allowed to warm to 0 °C during 2.5 h. The reaction was partitioned between hexanes (10 mL) and pH 7 phosphate buffer solution(10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL) and the combined organics were dried over $MgSO_4$ and concentrated. Flash chromatography afforded tetraene **58** (49 mg, 42 % yield).

Example 67

Synthesis of Alcohol (71).

A solution of **(+)-39** (106 mg, 0.13 mmol, prepared from commercially available methyl *(S)*-(+)-3-hydroxy-2-methyl propionate generally as described by Smith, et. al., *J. Am. Chem. Soc.* **1995**, *117*, 12011)) in CH_2Cl_2 was cooled to 0 °C and treated with neat diisobutylaluminum hydride (0.15 mL, 0.84 mmol). After 1 h, a solution of saturated aqueous potassium sodium tartrate (10 mL) was added (dropwise until cessation of hydrogen evolution) and the resultant biphasic mixture was stirred 4 h at ambient temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (15% ethyl acetate/hexanes) afforded alcohol **71** (88 mg, 83%) as a colorless oil: ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.26-7.20 (m, 4 H), 6.87-6.82 (m, 4 H), 5.03 (br d, J = 10.2 Hz, 1 H), 4.50 (AB_q, J = 10.5 Hz, Dv = 12.1 Hz, 2 H), 4.37 (AB_q, J =

11.6 Hz, Dv = 14.2 Hz, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.74 (m, 1 H), 3.57 (quintet, J = 10.5 Hz, 1 H), 3.51 (dd, J = 5.1, 3.7 Hz, 1 H), 3.47 (dd, J = 9.1, 4.9 Hz, 1 H), 3.38 (dd, J = 6.0, 4.6 Hz, 1 H), 3.35 (t, J = 5.5 Hz, 1 H), 3.20 (t, dd, J = 8.9, 8.6 Hz, 1 H), 2.68 (br t, J = 5.5 Hz, 1 H), 2.51 (m, 1 H), 2.22 (br t, J = 12.4 Hz, 1 H), 2.00-1.84 (m, 4 H), 1.74 (br d, J = 12.5 Hz, 1 H), 1.58 (d, J = 0.9 Hz, 3 H), 1.04 (d, J = 7.3 Hz, 3 H), 1.02 (d, J = 7.2 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.92 (s, 9 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 3 H), 0.1 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.4, 159.0, 131.64, 131.60, 131.0, 130.4, 129.3, 129.0, 113.9, 113.7, 86.2, 78.4, 77.5, 75.2, 72.7, 72.6, 65.4, 55.3, 39.9, 38.7, 37.5, 36.7, 35.7, 35.2, 26.2, 26.1, 23.1, 18.5, 18.4, 17.0, 15.7, 14.6, 13.7, 11.4, -3.3, -3.4, -3.9.

Example 68

Synthesis of Aldehyde (72).

A solution of alcohol **71**(88 mg, 0.108 mmol) and triethylamine (0.075 mL, 0.54 mmol) in CH_2Cl_2 (2 mL) and dimethylsulfoxide (1 mL) was treated with sulfur trioxide-pyridine (55 mg, 0.34 mmol). After 90 min, the mixture was diluted with ether (30 mL), washed with water (10 mL), aqueous $NaHSO_4$ (0.1 M, 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% ethyl acetate/hexanes) afforded **72** (84 mg, 96% yield) as a colorless oil: ^1H NMR (500 MHZ, $CDCl_3$) d 9.79 (d, J = 2.4 Hz, 1 H), 7.24-7.18 (m, 4 H), 6.87-6.82 (m, 4 H), 5.03 (br d, J = 10.2 Hz, 1 H), 4.46 (AB_q, J = 10.8 Hz, Dv = 7.1 Hz, 2 H), 4.37 (AB_q, J = 11.6 Hz, Dv = 14.0 Hz, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.57 (m, 2 H), 3.47 (dd, J = 9.1, 5.0 Hz, 1 H), 3.39 (dd, J = 5.9, 4.7 Hz, 1 H), 3.21 (t, J = 8.7 Hz, 1 H), 2.73 (m, 1 H), 2.51 (m, 1 H), 2.25 (t, J = 12.4 Hz, 1 H), 1.99-1.86 (m, 3 H), 1.70 (br d, J = 12.4 Hz, 1 H), 1.58 (s, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.92 (s, 9 H),

0.88 (d, J = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.74 (d, J = 6.8 Hz, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 204.5, 159.3, 159.0, 131.7, 131.5, 131.0, 130.3, 129.1, 129.0, 113.8, 113.7, 82.6, 78.4, 77.2, 74.4, 72.7, 72.5, 55.25, 55.24, 49.5, 40.3, 38.7, 36.7, 35.7, 35.0, 26.2, 26.1, 23.1, 18.5, 18.4, 17.0, 14.6, 13.4, 12.2, 11.4, -3.3, -3.4, -3.89, -3.91.

Example 69

Synthesis of Triene (73).

A solution lithium aluminum hydride (1.0 M in ether, 0.022 mL, 0.022 mmol).was added dropwise to a vigorously stirred suspension of chromium(III) chloride (40 mg, 0.25 mmol) in anhydrous THF (2 mL) at 0 °C. The resultant solution was stirred 45 min at room temperature and re-cooled to 0 °C. Aldehyde **72** (50 mg, 0.061 mmol) was added in THF (3 mL) via cannula. After 10 min, a mixture of 3-bromo-1-trimethylsilyl-1-propene and 3-bromo-3-trimethlsilyl-1-propene (3:1, 0.025 mL, 0.13 mmol) was added. The reaction mixture was further stirred 30 min at 0 °C and at ambient temperature for 12 h. Methanol (1 mL) and aqueous potassium hydroxide solution (6 M, 2 mL) were added and the resultant solution was stirred 1 h at ambient temperature. The aqueous layer was extracted with hexanes (3 x 15 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. Flash chromatography provided triene **73** (47 mg, 92%) as a single geometric isomer: ^1H NMR (500 MHZ, $CDCl_3$) d 7.27-7.20 (m, 4 H), 6.87-6.82 (m, 4 H), 6.57 (dt, J = 16.8, 10.4 Hz, 1 H), 6.00 (t, J = 11.0 Hz, 1 H), 5.55 (t, J = 10.5 Hz, 1 H), 5.18 (dd, J = 16.8, 1.6 Hz, 1 H), 5.09 (d, J = 10.1 Hz, 1 H), 4.96 (d, J = 10.2 Hz, 1 H), 4.50 (AB_q, J = 10.6 Hz, Dv = 43.6 Hz, 2 H), 4.36 (AB_q, J = 11.6 Hz, Dv = 16.9 Hz, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.44 (m, 2 H), 3.36 (dd, J = 6.4, 4.4 Hz, 1 H), 3.24 (dd, J = 7.4, 3.7 Hz, 1 H), 3.19 (t, J = 8.8 Hz, 1 H), 2.98 (m, 1 H), 2.44 (m, 1 H), 2.03 (t, J =

12.4 Hz, 1 H), 1.95 (m, 1 H), 1.84-1.72 (m, 2 H), 1.65 (br d, J = 11.4 Hz, 1 H), 1.52 (s, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.93 (s, 9 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.70 (d, J = 6.7 Hz, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.01 (s, 6 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 159.1, 159.0, 134.5, 132.2, 131.8, 131.2, 131.1, 129.1, 129.0, 117.6, 113.7, 84.6, 78.4, 77.2, 75.0, 72.7, 72.5, 55.3, 40.1, 38.9, 36.1, 35.5, 35.4, 26.3, 26.1, 23.0, 18.7, 18.6, 18.4, 17.2, 14.7, 14.4, 10.6, -3.2, -3.3, -3.89, -3.92.

Example 70

Synthesis of Alcohol (74).

Method A: Bis-ether **73** is dissolved in a mixture of CH_2Cl_2 and water (19:1) and cooled to 0 °C. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1 eq) is added and the resultant solution is stirred 2 h at 0 °C. The reaction mixture is diluted with hexanes and washed with aqueous sodium hydroxide solution, dried over $MgSO_4$ and concentrated. Flash chromatography affords **74**.

Method B: A solution of **73** and ethanethiol in CH_2Cl_2 is cooled to -78 °C and treated with a Lewis acid (e.g. magnesium bromide, borontrifluoride etherate, tin(IV) chloride, titanium(IV) chloride, etc.). The resultant solution is allowed to slowly warm until reaction ensues. The reaction is then quenched with aqueous sodium hydroxide solution, washed with water and brine, dried over $MgSO_4$, concentrated and chromatographed to afford **74**: ^{1}H NMR (500 MHZ, $CDCl_3$) d 7.27 (br d, J = 8.6 Hz, 2 H), 6.87 (br d, J = 8.6 Hz, 2 H), 6.60 (dt, J = 16.8, 10.5 Hz, 1 H), 6.04 (t, J = 11.0 Hz, 1 H), 5.57 (t, J = 10.5 Hz, 1 H), 5.55 (dd, J = 16.8, 1.8 Hz, 1 H), 5.12 (d, J = 10.3 Hz, 1 H), 4.97 (d, J = 10.2 Hz, 1 H), 4.51 ($AB_{quartet}$, J = 10.6 Hz, Dv = 47.6 Hz, 2 H), 3.80 (s, 3 H), 3.66 (dt, J = 10.9, 4.3 Hz, 1 H), 3.50 (m, 1 H), 3.44 (dd, J = 4.8, 4.0 Hz, 1 H), 3.39 (dd, 6.9, 3.8 Hz, 1 H), 3.25 (dd, J = 7.4, 3.7 Hz, 1 H), 3.00 (m, 1

H), 2.54 (m, 1 H), 2.31 (br t, J = 5.5 Hz, OH), 2.05 (t, J = 12.4 Hz, 1 H), 1.85-1.73 (m, 3 H), 1.67 (br d, J = 13.4 Hz, 1 H), 1,56 (s, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.95 (s, 9 H), 0.92 (s, 9 H), 0.91 (d, = 6.6 Hz, 3 H), 0.72 (d, J = 6.7 Hz, 3 H), 0.10 (s, 9 H), 0.07 (s, 3 H).

Example 71

Synthesis of Phosphonium Salt (75).

Iodine (127 mg, 0.50 mmol) was added in one portion to a vigorously stirred solution of alcohol **74** (120 mg, 0.167 mmol), triphenylphosphine (156 mg, 0.595 mmol), and imidazole (40 mg, 0.59 mmol) in benzene/ether (1:1) at -10 °C. The resultant solution was stirred 30 min at -10 °C and 30 min at ambient temperature, was diluted with 30 mL hexanes and was washed with water (2 x 10 mL), saturated aqueous sodium metabisulfite (10 mL), saturated aqueous sodium bicarbonate (10 mL) and saturated brine (10 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (2% ether/hexanes) provided a colorless oil. The oil was combined with diisopropylethylamine (0.015 mL, 0.086 mmol), triphenylphosphine (199 mg, 0.758 mmol), and benzene/toluene (7:3, 1.0 mL) in a plastic syringe and was subjected to a pressure of 12.8 Kbar. After 16 days, the reaction mixture was concentrated and chromatographed (10% acetonitrile/chloroform) to afford phosphonium salt **75** (126 mg, 76% for two steps) as a pale yellow film: ^1H NMR (500 MHZ, $CDCl_3$) d 8.84-7.65 (m, 15 H), 7.27 (br d, J = 8.6 Hz, 2 H), 6.87 (br d, J = 8.6 Hz, 2 H), 6.54 (dt, J = 16.8, 10.5 Hz, 1 H), 5,89 (t, J = 11.0 Hz, 1 H), 5.51 (t, J = 10.5 Hz, 1 H), 5.30 (d, J = 10.5 Hz, 1 H), 5.21 (d, J = 16.8, 1 H), 5.08 (d, J = 10.2 Hz, 1 H), 4.51 (AB_q, J = 10.4 Hz, Dv = 55.6 Hz, 2 H), 3.78 (s, 3 H), 3.76-3.68 (m, 2 H), 3.42 (dd, J = 5.4, 3.1 Hz, 1 H), 3.25-3.17 (m, 2 H), 2.97 (m, 1 H), 2.41 (m, 1 H), 2.06 (m, 1 H), 1.95 (t, J = 12.3 Hz, 1 H), 1.77-1.72 (m, 2 H), 1.58 (br d, J = 11.9 Hz, 1 H), 1.53 (s,

3 H), 1.10 (d, J =6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.91 (s, 9 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.86 (s, 9 H), 0.69 (d, J = 6.9 Hz, 3 H), 0.66 (d, J = 6.7 Hz, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.04 (s, 3 H), -0.05 (s, 3 H).

Example 72

Synthesis of Alcohol (+)-59.

At 0 °C, a solution of PMB ether **(+)-58** (4.0 mg, 3.55 mmol) in CH_2Cl_2 (0.5 mL) was treated with H_2O (50 mL) and DDQ (3.0 mg, 13.2 mmol). The mixture was stirred for 1 h and then diluted with ethyl acetate (30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Pipette flash chromatography (2% ethyl acetate/hexanes) provided **59** (3.4 mg, 95% yield) as a colorless oil: ^{1}H NMR (500 MHZ, $CDCl_3$) d 6.61 (ddd, J = 16.8, 10.9, 10.9 Hz, 1 H), 6.13 (apparent t, J = 11.0 Hz, 1 H), 5.32 (apparent t, J = 10.5 Hz, 1 H), 5.28 (dd, J = 11.1, 7.9 Hz, 1 H), 5.24-5.21 (m, 1 H), 5.19 (apparent t, J = 10.3 Hz, 1 H), 5.14 (d, J = 10.2 Hz, 1 H), 5.06 (d, J = 10.0 Hz, 1 H), 4.76 (apparent t, J = 9.3 Hz, 1 H), 4.50 (apparent t, J = 9.9 Hz, 1 H), 3.62 (apparent t, J = 2.4 Hz, 1 H), 3.60 (dd, J = 5.5, 3.4 Hz, 1 H), 3.32 (br d, J = 5.3 Hz, 1 H), 3.24 (apparent t, J = 5.1 Hz, 1 H), 2.79 (ddq, J = 9.9, 6.7, 6.7 Hz, 1 H), 2.60 (qd, J = 7.6, 2.7 Hz, 1 H), 2.63-2.57 (m, 1 H), 2.50-2.45 (m, 1 H), 2.16 (apparent t, J = 12.3 Hz, 1 H), 1.90-1.77 (m, 3 H), 1.75-1.69 (m, 2 H), 1.57 (s, 3 H), 1.60-1.50 (m, 1 H), 1.20 (d, J = 7.6 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.95-0.93 (m, 6 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.89-0.84 (m, 3 H), 0.87 (s, 9 H), 0.85 (s, 9 H), 0.73 (d, J = 6.8 Hz, 3 H), 0.07 (apparent s, 6 H), 0.052 (s, 3 H), 0.051 (s, 3 H), 0.04 (apparent s, 6 H), 0.03 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.3, 134.7, 133.5, 132.5, 132.1, 132.0, 131.5, 131.0, 118.4, 80.5, 78.8, 76.4, 74.9, 64.7, 44.1, 42.7, 38.0, 37.4,

36.3, 36.1, 35.2, 35.1, 34.2, 26.3, 26.2, 25.9, 25.7, 23.2, 18.5, 18.1, 18.0, 17.3, 17.2, 16.4, 16.1, 14.1, 13.7, 9.4, -3.0, -3.3, -3.6, -4.34, -4.36, -4.5, -4.8; high resolution mass spectrum (FAB, NBA) *m/z* 1029.7273 [$(M+Na)^+$; calcd for $C_{56}H_{110}O_7Si_4Na$: 1029.7226].

Example 73

Synthesis of Carbamate (+)-60

A solution of alcohol **59** (2.2 mg, 2.19 mmol) in CH_2Cl_2 (0.5 mL) was treated with trichloroacetyl isocyanate (20 mL, 0.17 mmol) at room temperature for 30 min. CH_2Cl_2 (2.0 mL) and neutral alumina (500 mg) were then added and the mixture was stirred at room temperature for 2 h, filtered through a short plug of silica, and concentrated. Pipette flash chromatography (10% ethyl acetate/hexane) furnished **60** (1.9 mg, 83% yield) as a colorless oil: IR (film, NaCl) 3510 (m), 3360 (m, br), 3180 (m), 2960 (s), 2930 (s), 2880 (s), 2855 (s), 1730 (s, br), 1596 (m), 1460 (s), 1385 (s), 1362 (s), 1325 (m), 1255 (s), 1220 (m), 1100 (s), 1043 (s), 983 (m), 937 (m), 904 (m), 832 (s), 770 (s), 663 (m) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 6.58 (dddd, *J* = 16.8, 10.6, 10.6, 0.7 Hz, 1 H), 6.01 (apparent t, *J* = 11.0 Hz, 1 H), 5.36 (apparent t, *J* = 10.4 Hz, 1 H), 5.27 (dd, *J* = 11.1, 7.9 Hz, 1 H), 5.22-5.16 (m, 2 H), 5.12 (d, *J* = 10.1 Hz, 1 H), 5.03 (d, *J* = 10.0 Hz, 1 H), 4.76 (apparent t, *J* = 9.2 Hz, 1 H), 4.71 (apparent t, *J* = 6.1 Hz, 1 H), 4.50 (ddd, *J* = 10.5, 10.5, 1.3 Hz, 1 H), 4.44 (br s, 2 H), 3.62 (apparent t, *J* = 2.4 Hz, 1 H), 3.42 (apparent t, *J* = 4.5 Hz, 1 H), 3.22 (apparent t, *J* = 5.3 Hz, 1 H), 2.98 (ddq, *J* = 10.1, 6.6, 6.6 Hz, 1 H), 2.60 (qd, *J* = 7.6, 2.7 Hz, 1 H), 2.63-2.55 (m, 1 H), 2.48-2.41 (m, 1 H), 2.09 (apparent t, *J* = 12.4 Hz, 1 H), 1.93-1.88 (m, 1 H), 1.87-1.77 (m, 2 H), 1.71 (ddd, *J* = 14.1, 10.8, 1.6 Hz, 1 H), 1.67 (br d, *J* = 13.7 Hz, 1 H), 1.56 (apparent s, 3 H), 1.55-1.50 (m, 1 H),

1.21 (d, J = 7.6 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 7.5 Hz, 3 H), 0.918 (d, J = 6.8 Hz, 3 H), 0.915 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.853 (d, J = 6.4 Hz, 3 H), 0.847 (s, 9 H), 0.70 (d, J = 6.8 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.053 (s, 3 H), 0.051 (s, 3 H), 0.040 (s, 3 H), 0.037 (s, 3 H), 0.03 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.3, 156.9, 133.6, 133.5, 132.4, 132.1, 131.9, 131.4, 129.8, 118.0, 80.5, 78.9, 74.9, 64.6, 44.2, 42.7, 37.8, 37.4, 36.0, 35.3, 35.2, 34.5, 34.2, 26.3, 26.2, 25.9, 25.7, 23.0, 18.5, 18.4, 18.1, 18.0, 17.5, 17.1, 16.44, 16.38, 14.1, 13.7, 10.1, -3.0, -3.4, -3.6, -4.4, -4.5, -4.8; high resolution mass spectrum (FAB, NBA) m/z 1072.7264 [$(M+Na)^+$; calcd for $C_{57}H_{111}NO_8Si_4Na$: 1072.7283].

Example 74

Synthesis of (+)-Discodermolide.

Tetrasilyl derivative **(+)-60** (5.8 mg, 5.5 mmol) was dissolved in 48% HF-CH_3CN (1:9, 1.0 mL) at room temperature. After12 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated.. Pipette flash chromatography (gradient elution; 1:30 -> 1:6 MeOH/$CHCl_3$) gave (+)-**1** (2.0 mg, 60% yield) as a white amorphous solid: $[\alpha]_D^{23}$ +15 ° © 0.033, MeOH); IR ($CHCl_3$) 3690 (w), 3620 (w), 3540 (w), 3430 (w), 3020 (s), 2975 (m), 2935 (m), 1740 (m), 1590 (w), 1540 (w), 1520 (w), 1467 (w), 1430 (w), 1385 (m), 1330 (w), 1233 (s), 1210 (s), 1100 (w), 1045 (m), 1033 (m), 975 (w), 930 (m), 910 (w), 793 (m), 777 (m), 765 (m), 750 (m), 705 (m), 687 (m), 670 (m), 660 (m), 625 (w) cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) d 6.60 (dddd, J = 16.8, 8.4, 8.4, 0.8 Hz, 1 H), 6.02 (apparent t, J = 11.1 Hz, 1 H), 5.51 (dd, J = 11.2, 7.9 Hz, 1 H), 5.42 (ddd, J = 10.6, 10.6, 0.6 Hz, 1 H), 5.34 (apparent t, J = 10.4 Hz, 1 H), 5.20 (dd, J =

16.9, 1.9 Hz, 1 H), 5.16 (d, J = 10.0 Hz, 1 H), 5.11 (d, J = 10.1 Hz, 1 H), 4.77-4.69 (m, 1 H), 4.70 (dd, J = 7.3, 4.2 Hz, 1 H), 4.60 (ddd, J = 10.0, 10.0, 2.4 Hz, 1 H), 4.56 (br s, 2 H), 3.73 (m, 1 H), 3.28 (m, 1 H), 3.18 (dd, J = 6.8, 4.8 Hz, 1 H), 2.98 (ddq, J = 10.1, 6.9, 6.9 Hz, 1 H), 2.78 (ddq, J = 9.8, 6.8, 6.8 Hz, 1 H), 2.66 (qd, J = 7.3, 4.6 Hz, 1 H), 2.60-2.55 (m, 1 H), 2.10-1.80 (m, 10 H), 1.69 (ddd, J = 14.4, 10.3, 3.1 Hz, 1 H), 1.64 (d, J = 1.3 Hz, 3 H), 1.30 (d, J = 7.4 Hz, 3 H), 1.06 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHZ, $CDCl_3$) d 173.6, 157.0, 134.4, 133.7, 133.4, 132.9, 132.2, 129.9, 129.8, 117.9, 79.1, 78.9, 77.1, 75.7, 73.2, 64.4, 43.1, 41.0, 37.4, 36.1, 36.0, 35.8, 35.3, 34.8, 33.1, 23.3, 18.4, 17.4, 15.6, 15.5, 13.7, 12.5, 9.0; high resolution mass spectrum (FAB, NBA) *m/z* 616.3840 [$(M+Na)^+$; calcd for $C_{33}H_{55}NO_8Na$: 616.3826].

Example 75

I. General procedure for synthesis of siloxy aldehydes (85).

A. A solution of organolithium (M = Li, figure 41))of type **80-83** (20 mmol) in ether (40 mL) is added slowly to a 0 °C solution of benzyl (S)-(+)-glycidyl ether (9 mmol) in ether (20 mL). The reaction is allowed to warm to room temperature. After 18-24 h, the reaction mixture is quenched by the addition of tert-butyldimethylsilyl triflate (10 mmol) and poured into saturated aqueous sodium bicarbonate (100 mL). The aqueous layer is separated and extracted with ether (2 x 50 mL). The combined organics are washed with saturated aqueous brine (50 mL), dried over magnesium sulfate and concentrated in vacuo. The residue is purified by flash chromatography to afford an alpha-siloxy benzyl ether.

B. To a solution of the above benzyl ether (6 mmol) in ethyl acetate-ethanol (8:1, 90 mL) is added palladium on carbon (10% wet, 500 mg). The mixture is stirred under hydrogen atmosphere for 3-6 h, then filtered and concentrated in vacuo. The residue is purified by flash chromatography to afford an alcohol.

C. Aldehyde **85**.

Oxalyl chloride (1.5 mmol) is added dropwise to a -78 °C solution of dimethyl sulfoxide (3 mmol) in dichloromethane (4 mL). After 15 min, a -78 °C solution of the alcohol prepared in part B (1 mmol) in dichloromethane (2 mL) is added via canula. After an additional 15 min, diisopropylethylamine (4.5 mmol) is added and the reaction is gradually warmed to room temperature over 1 h and quenched with aqueous sodium bisulfate. The mixture is diluted with ether (50 mL) and is washed with water (2 x 30 mL), saturated aqueous brine (2 x 30 mL), is dried over magnesium sulfate and concentrated in vacuo. The residue is purified by flash chromatography to afford 85.

II. General procedure for the conversion of (85) to tetraene (86).

D. Phosphonium salt **75** (0.2 mmol) is dissolved in anhydrous tetrahydrofuran (2 mL) and chilled to 0 °C. A solution of potassium bis(trimethylsilyl)amide (0.2 mmol, 0.5 M in tetrahydrofuran) is added and the reaction mixture is stirred 30 min at 0 °C. After cooling to -78 °C, a solution of aldehyde 85 (0.1 mmol) in tetrahydrofuran (2 mL) is added and the mixture is stirred 10 min at -78 °C and 2 h at room temperature. Saturated aqueous ammonium chloride (2 mL) is added and the resultant mixture is extracted with ether (3 x 20 mL). The ethereal layer is washed with water (2 x 25 mL) and saturated aqueous brine (25 mL), dried over magnesium sulfate and concentrated in vacuo. The residue is purified by flash chromatography to afford a tetraene.

E. To a solution of the tetraene prepared in part

D (0.050 mmol) in dichloromethane (3 mL) at 0 °C is added water (0.050 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.018 mmol). After 1 h, the reaction mixture is diluted with ethyl acetate (50 mL), washed with saturated aqueous brine (3 x 25 mL), dried over magnesium sulfate and concentrated in vacuo. The residue is purified by flash chromatography to afford an alcohol.

F. To a solution of the alcohol prepared in part E (0.010 mmol) in dichloromethane (2 mL) is added trichloroacetyl isocyanate (1.00 mmol). After 30 min, the reaction mixture is diluted with dichloromethane (4 mL) and neutral alumina (1 g) is added. The resultant suspension is stirred an additional 4 h. The reaction mixture is filtered and the concentrated filtrate is chromatographed on silica gel to afford a carbamate.

G. Analog **86**.

A solution of the carbamate prepared in part F (0.010 mmol) in 48% hydrofluoric acid-acetonitrile (1:9, 2 mL) is stirred at ambient temperature. After 12 h, saturated aqueous sodium bicarbonate (25 mL) is added and the mixture is extracted with ethyl acetate (3 x 20 mL). The combined organics are dried over magnesium sulfate and concentrated in vacuo. The residue is purified by flash chromatography to afford **86**.

Aldol (-)-5: *PMB protection: p*-Methoxybenzyl alcohol (200 g, 1.45 mol) was added to a suspension of NaH (60% in mineral oil; 5.82 g, 0.146 mol) in anhydrous ether (450 mL) over 1 h at room temperature. The mixture was stirred 1 h further and cooled to 0 °C. Trichloroacetonitrile (158 mL, 1.58 mol) was then introduced over 80 min. After 1.5 h the solution was concentrated with the water bath temperature maintained below 40 °C. The residue was treated with a mixture of pentane (1.5 L) and MeOH (5.6 mL), stirred at room temperature for 30 min, and filtered through a short Celite column. Concentration gave

the trichloroimidate (370.9 g) as a yellow oil which was used without further purification.

A solution of Roush's ester (+)-6 (129.0 g, 1.09 mol) in CH_2Cl_2/cyclohexane (1:2, 1.5 L) was cooled to 0 °C and treated with crude trichloroimidate (370.9 g) and PPTS (13.69 g, 55.0 mmol) over 0.5 h. After 3 h, the mixture was warmed to room temperature, stirred for 40 h, and concentrated. Suction filtration through a short silica plug (5 X 6 '' sintered glass funnel; 20% ethyl acetate/hexanes) afforded the corresponding PMB ether (234.2 g) as a pale yellow oil which was divided into two portions for the next reaction.

Reduction: A solution of the above PMB ether(116.1 g) in anhydrous THF (800mL) was cooled to 0 °C and added via cannula to a solution of $LiAlH_4$ (0.67 M in THF, 800 mL, 0.536 mol) over 1 h (150 mL THF rinse), warmed gradually to room temperature, and stirred for 1 h. The reaction mixture was cooled to 0 °C and quenched via dropewise addition of H_2O (20 mL), 15% NaOH (20mL), then H_2O (60 mL). The resultant mixture was then treated with $MgSO_4$ (10 g), filtered (100 mL Et_2O rinse), and concentrated, furnishing a red oil (91.0 g). The remaining 118.1 g was processed using the same protocol to yield an additional 94 g, yielding a total of 185 g of the corresponding alcohol(+)-8, which was divided into three portions for the next two reactions.

Swern: A solution of DMSO (72.1 mL, 1.02 mol) in CH_2Cl_2 (1.5 L) was cooled to -78 °C and oxalyl chloride (44.3 mL, 0.51 mmol) was added over 30 min (internal temp < -65 °C). After an additional 30 min, a solution of the above alcohol(71.2 g, 0.338 mol) in CH_2Cl_2 (100 mL) was added dropwise via cannula down the side of the flask over 30 min (20-mL rinse). The resultant mixture was stirred 45 min further at -78 °C, then *i*-Pr_2NEt (345 mL, 2.03 mol) was added over 45 min. The mixture was stirred 30 min further at -78 °C then slowly warmed to 0 °C (internal temp) via removal of the external cooling bath. The reaction was quenched via

addition to a vigourously stirred aqueous $NaHSO_4$ solution (1.0 M, 2.0 L). The layers were separated, the aqueous phase extracted (3 X Et_2O). The combined organic layers were concentrated (30 °C water bath), diluted with ether (1000 mL), washed with aqueous $NaHSO_4$ (3 X), water (1 X), saturated aqueous $NaHCO_3$ (1 X), and brine (1 X). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the corresponding aldehyde (70.5 g, ca. 100%) as a colorless oil.

Evans Aldol Reaction: A solution of oxazolidinone **61** (90.7 g, 389 mmol) in degassed CH_2Cl_2 (972 mL, 4 Å MS dried, argon sparged) was cooled to -55 °C (internal temp) and *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 403 mL) was introduced over 0.5 h, followed by addition of NEt_3 (61.3 mL, 440 mmol) over 20 min. The mixture was warmed to 0 °C (internal temp), stirred for 10 min, and cooled to -70 °C. A degassed solution of above aldehyde (70.5 g, 0.338 mmol) in CH_2Cl_2 (200 mL) was then added via a cannula down the side of the flask over 1 h (20 mL rinse). After an additional 1.0 h at -78 °C, the reaction was warmed to -8 °C, stirred for 1 h, then quenched with pH 7 potassium phosphate monobasic-sodium hydoxide buffer (0.05 M, 220 mL). A solution of 30% H_2O_2 in MeOH (1:2, 700 mL) was added to the vigorously stirred reaction mixture at such a rate as to maintain an internal temp < 8 °C (60 min, -10 °C cooling bath). The reaction was stirred 10 h at room temperature, and concentrated to ca. 1000 mL. The residue was dissolved in 1500 mL of 10:1 Et_2O/CH_2Cl_2, and the resulting layers were separated. The aqueous layer was extracted (3 X 10:1 Et_2O/CH_2Cl_2), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (1000 mL), water (1000 mL) and saturated brine (2 x 500 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to ca. 400 mL (3 X using a 2000 mL rb). The resulting white solid was filtered and dried overnight to give analytically pure **62** (83.8g, 56%). The combined

mother liquors were concentrated and recrystallized from Et_2O to give an additional 10.0 g (7.0%, total yield of 63%) of **62**. The remaining 120 g of precursor alcohol was processed through the above two steps to give an additional 155.4 of **62** for a total of 249.2 g (52% yield over 4 steps). X-ray quality crystals were grown by recrystallization from ether-hexanes: mp 111.5-113.0 °C; $[\alpha]^{23}{}_D$ +34.3°; IR ($CHCl_3$) 3600-3400 (br), 1780, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.33 (m, 3 H), 7.28-7.21 (m, 4 H), 6.85 (m, 2 H), 5.59 (d, J = 6.9 Hz, 1 H), 4.72 (quintet, J = 6.6 Hz, 1 H), 4.43 (s, 2 H), 3.92 (qd, J = 6.8, 3.4 Hz, 1 H), 3.88 (dd, J = 8.2, 3.4 Hz, 1 H), 3.76 (s, 3 H), 3.69 (br s, OH), 3.55 (m, 2 H), 1.95 (m, 1 H), 1.20 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 159.3, 152.8, 133.3, 129.8, 129.4, 128.77, 128.7, 125.6, 113.8, 78.9, 75.6, 74.7, 73.2, 55.2, 55.1, 40.9, 36.0, 14.3, 13.6, 9.6; high resolution mass spectrum (CI) *m/z* 441.2133, [(M)+, calcd for $C_{25}H_{31}NO_6Na$: 441,2151]. Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N: 3.17. Found: C, 68.29; H, 7.17; N, 3.16.

Common Precursor (-)-5: At 0 °C, a suspension of *N,O*-dimethylhydroxylamine hydrochloride (50.8 g, 521 mmol) in THF (380 mL) was cautiously treated with $AlMe_3$ (2.0 M in hexane, 256 mL, 512 mmol) over 30 min. The resultant solution was stirred 30 min at 0 °C and 90 min at ambient temperature, and then cooled to -20 °C. A solution of oxazolidinone **62** (76.7 g, 174 mmol) in THF (380 mL) was introduced over 60 min via a cannula (20-mL rinse). After an additional 90 min at -20 °C, the solution was poured slowly into a solution of aqueous HCl (1.0 N, 1.0 L) and CH_2Cl_2 (1.0 L) and stirred vigorously at 0 °C for 90 min. The aqueous phase was extracted with CH_2Cl_2 (3 X1L) and the combined organic solutions were washed with water (2 X 500 mL) and saturated brine (500 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in a

minimal amount of ether. An equal volume of hexanes was added, and the resultant solution was refrigerated (4 °C) overnite. Filtration of the crystals afforded (4*R*, 5*S*)-4-methyl-5-phenyl-2-oxazolidinone (30.68 g, 100%). Concentration of the residual liquid and flash chromatography (20% acetone/hexanes) afforded **(-)-5** (55.5 g, 98% yield) as a colorless oil: $[\alpha]^{23}{}_{D}$ --3.6° (*c* 1.67, $CHCl_3$); IR ($CHCl_3$) 3470, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.44 (ABq, J_{AB} = 11.6 Hz, Δ_{AB} = 17.1 Hz, 2 H), 3.95 (d, *J* = 2.8 Hz, 1 H), 3.79 (s, 3 H), 3.70 (ddd, *J* = 8.2, 3.2, 3.2 Hz, 1 H), 3.66 (s, 3 H), 3.62 (dd, *J* = 9.0, 4.0 Hz, 1 H), 3.53 (dd, *J* = 9.1, 5.9 Hz, 1 H), 3.17 (s, 3 H), 3.04 (m, 1 H), 1.91-1.84 (m, 1 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 159.0, 130.6, 129.1, 113.7, 113.6, 73.8, 72.8, 72.6, 61.3, 55.1, 36.5, 36.0, 14.2, 10.4; high resolution mass spectrum (CI, NH_3) *m/z* 326.1962 [$(M+H)^+$; calcd for $C_{17}H_{28}NO_5$: 326.1967].
Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.74; H, 8.36. Found: C, 62.74; H, 8.24.

FRAGMENT A:

PMP Acetal (+)-11: At -10 °C, a vigorously stirred solution of common precursor (-)-**5** (21.55 g, 66.2 mmol) and powdered 4 Å molecular sieves (25 g) in CH_2Cl_2 (500 mL) was treated with DDQ (17.80 g, 78.4 mmol). The resultant mixture was warmed to 0 °C over 90 min and filtered through a pad of Celite (CH_2Cl_2 ,500 mL). The filtrate was washed with aqueous NaOH (1 N, 200 mL), concentrated to ca. 1/10 volume, diluted with hexanes (400 mL), washed with aqueous NaOH (2 x 100 mL) and saturated brine (2 X 200 mL), dried over $MgSO_4$, filtered and concentrated to afford a pale yellow-colored solid. Crystallization from hexanes-ether afforded (+)-**6** as colorless needles (15.90 g). Flash chromatography (25% ethyl acetate/hexanes) of the mother liquor provided an additional 2.50 g of (+)-**11** (86% total yield): mp 92.0-93.5

°C; $[\alpha]^{23}{}_{D}$ +36.4° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 3010, 1663, 1620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.46 (s, 1 H), 4.04 (dd, *J* = 11.3, 4.7 Hz, 1 H), 3.82 (dd, *J* = 9.8, 6.5 Hz, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.51 (apparent t, *J* = 11.2 Hz, 1 H), 3.19 (s, 3 H), 3.21-3.14 (m, 1 H), 1.98-1.92 (m, 1 H), 1.27 (d, *J* = 7.0 Hz, 3 H), 0.75 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 159.8, 131.2, 127.2, 113.5, 100.7, 82.8, 72.8, 61.3, 55.3, 39.0, 33.8, 32.6, 13.1, 12.4; high resolution mass spectrum (CI, NH_3) *m/z* 323.1736 [M^+; calcd for $C_{17}H_{25}NO_5$: 323.1732]. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79. Found: C, 63.18; H, 7.74.

Aldehyde (+)-12. A solution of amide (+)-**11** (16.4 g, 50.7 mmol) in THF (100 mL) was added *via* cannula over 15 min to a -60 °C solution of $LiAlH_4$ (3.09 g, 81.4 mmol) in THF (400 mL). The resultant solution was stirred 2 h at -60 °C, warmed 0 °C, stirred 60 min, and quenched via dropwise addition of glacial acetic acid (15.0 mL, 254 mmol), over 45 min. Saturated aqueous sodium potassium tartrate (500 mL) was added, and the resultant solution was vigorously stirred at ambient temperature. After 1 h, the reaction mixture was diluted with hexanes (500 mL), and the organic layer was separated and concentrated to ca. 1/2 volume *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL), and the combined organic layers were washed with water (200 mL), saturated brine (2 x 200 mL), and saturated $NaHCO_3$ (200 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated to give (+)-**11** as a white slurry (14.4g) that was used without further purification. An analytical sample was obtained by recrystallization from ether: mp 68-71 °C; $[\alpha]^{23}{}_{D}$ +16.2° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 1735, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (apparent s, 1 H), 7.32 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 5.46 (s, 1 H), 4.13

(dd, J = 11.5, 4.8 Hz, 1 H), 4.05 (dd, J = 10.4, 2.6 Hz, 1 H), 3.77 (s, 3 H), 3.56 (apparent t, J = 11.1 Hz, 1 H), 2.56 (qd, J = 7.1, 2.6 Hz, 1 H), 2.15-2.03 (m, 1 H), 1.23 (d, J = 7.1 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 159.9, 130.7, 127.2, 113.5, 100.9, 81.6, 72.8, 55.2, 47.4, 30.3, 11.9, 7.1; high resolution mass spectrum (CI, NH_3) *m/z* 265.1432 [$(M+H)^+$; calcd for $C_{15}H_{21}O_4$: 265.1439]. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.84; H, 7.50.

Aldol (-)-13. A solution of oxazolidinone (-)-**9** (17.8 g, 76.2 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 70.85 mL) was added over 0.5 h, followed by addition of NEt_3 (12.9mL, 92.7 mmol) over 20 min. The mixture was stirred at 0 °C for 1 h and cooled to -78 °C. A solution of aldehyde (+)-**12** (14.4 g) in CH_2Cl_2 (20 mL) was added over 10 min, and the mixture was stirred 20 min further at -78 °C, warmed to 0 °C and stirred for 1 h. The reaction was quenched with pH 7 potassium phosphate monobasic-sodium hydroxide buffer (0.05 M, 100 mL) and MeOH (300 mL) and cautiously treated with 30% H_2O_2 in MeOH (100 mL) at 0 °C with stirring. After 1 h, saturated aqueous $Na_2S_2O_3$ (100 mL) was added. Following concentration and extraction with ethyl acetate (3 x 250 mL), the combined extracts were washed with saturated aqueous $Na_2S_2O_3$, aqueous 10% $NaHCO_3$, brine (200 mL each), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (10% ethyl acetate/hexanes) provided (-)-**13** (20.9 g, 77%, two steps) as a white solid: mp 98-100 °C; $[\alpha]^{23}{}_D$ -13.5° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 3690, 3520 (br),1790, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 2 H), 7.31 (d, J = 7.6 Hz, 2 H), 7.27 (d, J = 7.2 Hz, 1 H), 7.19 (d, J = 7.7 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 5.45 (s, 1 H), 4.67-4.62 (m, 1 H), 4.14 (apparent d, J = 5.3 Hz, 2 H), 4.08

(dd, J = 11.4, 4.8 Hz, 1 H), 4.07 (apparent t, J = 4.1 Hz, 1 H), 4.04-3.99 (m, 1 H), 3.76 (s, 3 H), 3.61 (dd, J = 9.9, 2.2 Hz, 1 H), 3.51 (apparent t, J = 11.1 Hz, 1 H), 3.33 (d, J = 1.3 Hz, 1 H), 3.21 (dd, J = 13.4, 3.4 Hz, 1 H), 2.76 (dd, J = 13.4, 9.4 Hz, 1 H), 2.12-2.06 (m, 1 H), 1.92-1.86 (m, 1 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.74 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 160.0, 152.7, 135.0, 131.0, 129.4, 128.9, 127.40, 127.39, 113.6, 101.2, 85.8, 74.5, 73.0, 66.0, 55.2, 54.9, 39.8, 37.7, 35.7, 30.4, 12.8, 11.7, 7.8; high resolution mass spectrum (CI, NH_3) *m/z* 497.2410 [M^+; calcd for $C_{28}H_{35}NO_7$: 497.2413]. Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.58; H, 7.09. Found: C, 67.42; H, 7.02.

TBS Ether (-)-14: A solution of alcohol (-)-**13** (26.3 g, 52.9 mmol) and 2,6-lutidine (11.1 mL, 95.3 mmol) in CH_2Cl_2 (150 mL) was cooled to -20 °C and TBSOTf (20.5 mL, 79.3 mmol) was added over 30 min. After an additional 2 h at 0 °C, the mixture was diluted with ether (300 mL), washed with aqueous $NaHSO_4$ (1.0 M) and brine (200 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (gradient elution, 5 10% Æ ethyl acetate/hexanes) afforded (-)-**13** (32.4 g, 100% yield) as a colorless oil: $[\alpha]^{23}{}_{,D}$ -20.3° (c 1.32, $CHCl_3$); IR ($CHCl_3$) 1788, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.7 Hz, 2 H), 7.30-7.12 (m, 5 H), 6.82 (d, J = 8.7 Hz, 2 H), 5.44 (s, 1 H), 4.30 (ddt, J = 13.4, 7.3, 5.1, 1 H), 4.11 (dd, J = 7.1, 4.0 Hz, 1 H), 4.02 (dd, J = 11.2, 4.7 Hz, 1 H), 3.97 (dq, J = 7.0, 7.0 Hz, 1 H), 3.80 (dd, J = 8.9, 2.3 Hz, 1 H), 3.740 (apparent t, J = 4.9 Hz, 1 H), 3.738 (s, 3 H), 3.48 (apparent t, J = 11.1 Hz, 1 H), 3.27 (apparent t, J = 8.2 Hz, 1 H), 3.15 (dd, J = 13.4, 3.2 Hz, 1 H), 2.59 (dd, J = 13.4, 9.8 Hz, 1 H), 2.05 (apparent qd, J = 7.4, 4.2 Hz, 1 H), 2.02-1.94 (m, 1 H),

1.19 (d, J = 6.9 Hz, 3 H), 1.04 (d, J = 7.5 Hz, 3 H), 0.92 (s, 9 H), 0.73 (d, J = 6.7 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 159.9, 152.4, 135.5, 132.0, 129.4, 128.8, 127.8, 127.2, 113.4, 100.7, 80.7, 74.6, 73.1, 65.3, 55.3, 55.2, 41.4, 40.9, 37.4, 30.6, 26.0, 18.1, 15.0, 12.7, 11.5, -4.0, -4.6; high resolution mass spectrum (CI, NH_3) m/z 612.3340 [$(M+H)^+$; calcd for $C_{34}H_{50}NO_7Si$: 612.3356]. Anal. Calcd for $C_{34}H_{49}NO_7Si$: C, 66.74; H, 8.07. Found: C, 66.69; H, 7.98.

Alcohol (+)-15 At -30 °C, a solution of imide **(-)-14** (32.0 g, 52.3 mmol) in THF (600 mL) was treated with EtOH (6.14 mL, 105 mmol). $LiBH_4$ (2.0 M in THF, 52.3 mL, 105 mmol) was then added over 15 min. After an additional 1 h at 0 °C and 12 h at room temperature, the mixture was diluted with ether (1.0 L), quenched carefully with aqueous NaOH (1.0 N, 200 mL), and stirred at room temperature for 2 h. The layers were separated, and the organic phase was washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (20% ethyl acetate/hexanes) provided (+)-**15** (18.7 g, 81% yield) as a colorless oil that solidified upon standing. An analytical sample was obtained by recrystallization from hexane: mp 65.0-67.0 °C; $[\alpha]^{23}{}_{,D}$ or $[\alpha]_D^{23}$= +36.4° (c 1.57, $CHCl_3$); IR ($CHCl_3$) 3630, 3480 (br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 5.38 (s, 1 H), 4.08 (dd, J = 11.2, 4.7 Hz, 1 H), 3.84 (dd, J = 6.7, 1.9 Hz, 1 H), 3.77 (s, 3 H), 3.53 (dd, J = 9.9, 1.8 Hz, 1 H), 3.55-3.52 (m, 1 H), 3.47 (apparent t, J = 11.1 Hz, 1 H), 3.44 (dd, J = 10.3, 6.2 Hz, 1 H), 2.08-1.97 (m, 2 H), 1.94 (dqd, J = 7.1, 7.1, 1.7 Hz, 1 H), 1.76 (br s, 1 H), 1.02 (d, J = 7.1, 3 H), 0.88 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.73 (d, J = 6.7 Hz, 3 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 131.4, 127.3, 113.5, 101.0,

82.9, 74.3, 73.3, 66.3, 55.2, 38.7, 37.8, 30.7, 26.1, 18.3, 12.2, 11.1, 10.7, -4.0, -4.2; high resolution mass spectrum (CI, NH_3) *m/z* 439.2889 [$(M+H)^+$; calcd for $C_{24}H_{43}O_5Si$: 439.2879]. Anal. Calcd for $C_{24}H_{42}O_5Si$: C, 65.71; H, 9.65. Found: C, 65.51; H 9.54.

Iodide (+)-A. A vigorously stirred solution of alcohol (+)-**15** (4.70 g, 10.7 mmol), triphenylphosphine (4.21 g, 16.1 mmol) and imidazole (1.09 g, 16.1 mmol) in benzene/ether (1:2, 75 mL) was treated with iodine (4.08 g, 16.1 mmol). After 1 h, the mixture was diluted with ether (200 mL), washed with saturated $Na_2S_2O_3$ and brine (100 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (2% ethyl acetate/hexanes) furnished (+)-**A** (5.56 g, 95% yield) as a colorless oil that solidified on standing. Recrystallization from ethanol afforded colorless needles: mp 43-44 °C; $[\alpha]^{23}{}_{D}$ +51.3° (*c* 1.22, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 5.40 (s, 1 H), 4.09 (dd, *J* = 11.2, 4.7 Hz, 1 H), 3.85 (dd, *J* = 7.1, 1.9 Hz, 1 H), 3.79 (s, 3 H), 3.48 (dd, *J* = 8.2, 1.5 Hz, 1 H), 3.47 (apparent t, *J* = 11.1 Hz, 1 H), 3.18-3.12 (m, 2 H), 2.11-2.00 (m, 2 H), 1.84 (dqd, *J* = 7.1, 7.1, 1.6 Hz, 1 H), 1.02 (d, *J* = 7.1 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.72 (d, *J* = 6.7 Hz, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 131.4, 127.4, 113.4, 100.9, 82.4, 75.5, 73.2, 55.3, 39.6, 38.7, 30.7, 26.2, 18.4, 14.7, 14.5, 12.2, 10.7, -3.7, -3.8; high resolution mass spectrum (CI, NH_3) *m/z* 548.1833 [M^+; calcd for $C_{24}H_{41}IO_4Si$: 548.1819]. Anal. Calcd for $C_{24}H_{41}O_4ISi$: C, 52.55; H, 7.53. Found: C, 52.77; H, 7.68.

FRAGMENT B:

TBS Ether (-)-17: A solution of common precursor (-)-**5** (48.0 g, 148 mmol) and 2,6-lutidine (30.1 mL, 258

mmol) in CH_2Cl_2 (370 mL) was cooled to -20 °C (1:1 acetone/water) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (38.6 mL, 168 mmol) was added over 20 min. The mixture was stirred for 1.5 h, diluted with cold Et_2O (800 mL, 0 °C), poured into 300 mL of 1 M $NaHSO_4$, and the resulting layers were separated . The aqueous layer was extracted (3 X Et_2O), and the combined organic layers were washed with aqueous1.0 M $NaHSO_4$ (4 X), water, saturated $NaHCO_3$ (2 X), and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield (-)-**17** (65.1 g, 100%, purity >95% by ^{1}H NMR) as a clear, colorless oil. An analytical sample was prepared via flash chromatography (10% ethyl acetate/hexanes): $[\alpha]^{23}{}_{D}$ -9.5° (*c* 1.84, $CHCl_3$); IR ($CHCl_3$) 1658 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2 H), 6.83 (d, J = 8.7, 2 H), 4.36 (ABq, J_{AB} = 11.6 Hz, Δ_{AB} = 17.3 Hz, 2 H), 3.92 (dd, J = 8.2, 3.0 Hz, 1 H), 3.77 (s, 3 H), 3.55 (s, 3 H), 3.54 (dd, J = 9.2, 2.5 Hz, 1 H), 3.13 (dd, J = 9.2, 7.8 Hz, 1 H), 3.09 (s, 3 H), 3.15-3.09 (m, 1 H), 1.92-1.87 (m, 1 H), 1.09 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.04 (apparent s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 159.1, 130.9, 129.2, 113.7, 76.0, 72.7, 71.9, 61.1, 55.2, 39.3, 38.9, 26.1, 18.4, 15.3, 15.0, -3.87, -3.93; high resolution mass spectrum (CI, NH_3) *m/z* 440.2823 [$(M+H)^+$; calcd for $C_{23}H_{42}NO_5Si$: 440.2832]. Anal. Calcd for $C_{23}H_{41}NO_5Si$: C, 62.83; H, 9.40. Found: C, 63.05; H, 9.32.

Aldehyde (-)-18: At -78 °C, a solution of amide (-)-**17** (9.19 g, 20.9 mmol) in THF (750 mL, dried over 4 Å MS) was treated with DIBAL-H (1.0 M in hexane, 115.0 mL) via dropwise addition down the sides of the flask (30 min addition time). The reaction was stirred for an additional 3 h and quenched with MeOH (8 mL). The -78 °C reaction mixture was poured into saturated aqueous Rochelle's salt (1000 mL) and diluted with Et_2O (1500 mL). After stirring at

rt for 30 min, the mixture was poured into a separatory funnel and virourously shaken to break up the emulsion. The layers were separated, and the combined organic layers were washed with saturated aqueous Rochelle's salt, water, saturated $NaHCO_3$, and brine (2 X 300 mL each). The organic layer was dried over $MgSO_4$, filtered and concentrated to give (-)-**18** (31 g, 100%) as a clear, colorless oil, which was taken on to the next step without further purification. An analytical sample was obtained via flash chromatography (10% ethyl acetate/hexanes): $[\alpha]^{23}{}_{D}$ -22.9° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, J = 0.9 Hz, 1 H), 7.22 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.37 (ABq, J_{AB} = 11.6 Hz, Dn_{AB} = 23.6 Hz, 2 H), 4.18 (dd, J = 6.1, 3.7 Hz, 1 H), 3.78 (s, 3 H), 3.41 (dd, J = 9.2, 5.7 Hz, 1 H), 3.31 (dd, J = 9.2, 6.0 Hz, 1 H), 2.47 (qdd, J = 7.1, 3.7, 0.9 Hz, 1 H), 2.03-1.95 (m, 1 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.84 (s, 9 H), 0.04 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 159.2, 130.5, 129.2, 113.8, 72.7, 72.4, 71.7, 55.3, 50.0, 38.3, 25.9, 18.2, 14.3, 8.4, -4.1, -4.4; high resolution mass spectrum (FAB, NBA) *m/z* 403.2304 [$(M+Na)^+$; calcd for $C_{21}H_{36}O_4SiNa$: 403.2280].

Fragment B (+)-3: At -23 °C, a suspension of $EtPh_3PI$ (68.7g, 164 mmol, dried at 70 °C/0.2 Torr for 2 h) in THF (600 mL, dried over 4 Å MS, sparged with argon) was treated with *n*-BuLi (2.5 M in hexane, 64.0 mL, 160.1 mmol) over 30 min to form a dark red solution. After an additional 10 min, the red ylide solution was added over 40 min via cannula to a cooled (-78 °C) *solution* of I_2 (41.7 g, 164.2 mmol) in THF (1400 mL, solution prepared by adding I_2 to degassed THF at rt and vigorously stirring for 40 min before cooling) such that the internal temperature does not exceed -70 °C. The resultant yellow slurry was stirred at -75 °C (internal) for 5 min and warmed to -23 °C (internal).

NaHMDS (1.0 M in THF, 147 mL) was added via cannula over 30 min, and the resulting orange suspension was stirred 15 min further and cooled to -33 °C (internal). A solution of crude aldehyde **(-)-13** (31.2 g, 82.1 mmol) in THF (200 mL) was introduced via cannula over 15 min, and the reaction mixture was stirred at -30 °C for an additional 45 min, warmed to 7 °C over 1 h, and quenched with MeOH (20 mL). Following concentration and suction filtration through a 6 X 8'' silica plug (100% Et_2O,2000 mL suction filtration sintered glass frit), the filtrate was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (15% CHCl/hexanes; then gradient elution 1% ethyl acetate/hexanes 32% ethyl acetate/hexanes) furnished **(+)-3** (19.6 g, 46% yield for two steps, 9:1 *Z/E*) as a clear, colorless oil). An analytical sample of the *Z* isomer was obtained by reversed-phase HPLC (gradient elution; 90% CH_3CN/H_2O *E* 100% CH_3CN): colorless oil; $[\alpha]^{23}{}_{,D}$ +23° (*c* 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) d 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.28 (apparent dd, *J* = 8.9, 1.4 Hz, 1 H), 4.41 (ABq, J_{AB} = 7.0 Hz, Dn_{AB} = 10.2 Hz, 2 H), 3.80 (s, 3 H), 3.60 (apparent t, *J* = 5.3 Hz, 1 H), 3.51 (dd, *J* = 9.1, 5.1 Hz, 1 H), 3.23 (dd, *J* = 9.0, 8.0 Hz, 1 H), 2.54-2.47 (m, 1 H), 2.44 (d, *J* = 1.4 Hz, 3 H), 2.00-1.92 (m, 1 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 159.1, 139.6, 131.0, 129.1, 113.7, 98.9, 76.5, 72.6, 72.5, 55.3, 44.5, 38.7, 33.5, 26.1, 18.4, 14.7, 14.5, -3.95, -3.99; high resolution mass spectrum (FAB, NBA) *m/z* 541.1626 [$(M+Na)^+$; calcd for $C_{23}H_{39}IO_3SiNa$: 541.1611].

FRAGMENT C: Aldehyde (-)-27: A mixture of PMB ether (-)-5 (4.27 g, 9.71 mmol), Pearlman's catalyst (20% $Pd(OH)_2/C$, 1.60 g) and EtOH (120 mL) was stirred for 9 h

under H_2 (balloon) at room temperature, filtered and concentrated. The resulting alcohol (-)-**13** (3.84 g, containing *p*-methoxyanisole) was used without further purification. At 0 °C, a solution of crude **alcohol**(3.84 g) and Et_3N (6.4 mL, 46 mmol) in CH_2Cl_2 (24 mL) and DMSO (48 mL) was treated with SO_3.pyridine (5.7 g, 36 mmol). After 90 min, the mixture was diluted with ether (150 mL), washed with H_2O (100 mL), aqueous $NaHSO_4$ (1.0 M, 100 mL), H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (20% ethyl acetate/hexanes) afforded (-)-**27** (2.88 g, 93% yield) as a colorless oil that solidified on standing at 0 °C. Recrystallization (hexanes) afforded colorless plates: mp 45-46 °C; $[\alpha]^{23}{}_{,D}$ -65.0° (*c* 1.38, $CHCl_3$); IR ($CHCl_3$) 1750, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.6 Hz, 1 H), 4.22 (dd, *J* = 8.9, 2.6 Hz, 1 H), 3.68 (s, 3 H), 3.10 (apparent s, 4 H), 2.46 (qdd, *J* = 7.1, 2.6, 1.5 Hz, 1 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.10 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.092 (s, 3 H), 0.088 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 175.6, 75.1, 61.5, 52.1, 39.6, 32.1, 25.9, 18.2, 15.4, 10.2, -4.07, -4.11; high resolution mass spectrum (CI, NH_3) *m/z* 318.2096 [$(M+H)^+$; calcd for $C_{15}H_{32}NO_4Si$: 318.2100].

Enone (-)-64: To a -78 °C solution of diisopropylamine (14.24 mL, 104.1 mmol) in THF (77 mL) was added *n*-BuLi (2.5M in hexanes, 43 mL, 107.6 mmol). The mixture was slowly warmed to -30 °C over 30 min, stirred at 0 °C for 15 min, then cooled to -78 °C. Neat mesityl oxide was then added (7.94 mL, 69.4 mmol), stirred for 5 min, followed by dropwise addition of trimethylsilylchloride (15.51 mL, 122.19 mmol). The mixture was stirred 5 min, quenched with 15 mL saturated $NaHCO_3$ solution, and diluted with 50 mL pentane. The mixture was washed (H_2O), separated, and the aqueous layer was extracted with pentane (2 X 30 mL). The combined organic extracts were dried ($MgSO_4$),

filtered, and concentrated. Distillation (70 °C @ 30 Torr) provided 7.55 g (15:1 mixture)of **63** as a clear oil.

To a -78 °C solution of aldehyde (-)-**27** (7.15 g, 22.5 mmol) in CH_2Cl_2 (50 mL) was added (dropwise over 20 min) $TiCl_4$ (1M in CH_2Cl_2, 22.7 mL, 22.7 mmol). The resultant solution was stirred 10 min at -78 °C, then neat **63** (4.67 g, 27.4 mmol) was added dropwise over 2 min (rinse 2 X 5mL) and the reaction mixture was further stirred at -78 °C for 2 h. The solution was next poured into a solution comprised of pH 8 phosphate buffer (130 mL) and saturated aqueous $NaHCO_3$ solution (66 mL) and stirred for 10 min. The aqueous layer was seperated and extracted with CH_2Cl_2 (2 X 250 mL). The combined organic layers were washed (H_2O, 250 mL), diluted (hexanes, 200 mL) and treated with 1 mL of trifluoroacetic acid. The solution was stirred 10 min at ambient temperature, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (gradient elution,1-10% EtOAc/hexanes) afforded (-)-**64** (5.72 g, 72%) as a white solid: mp 53-55 °C; $[\alpha]^{23}{}_{D}$ -10.6° (*c* 0.88, $CHCl_3$); IR ($CHCl_3$) 1728, 1719, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (m, 1 H), 4.78 (ddd, J = 10.0, 6.6, 4.3 Hz, 1 H), 3.65 (t, J = 2.8 Hz, 1 H), 2.72 (dd, J = 15.8, 4.3 Hz, 1 H), 2.66 (dd, J = 15.8, 6.7 Hz, 1 H), 2.62 (qd, J = 7.6, 3.2 Hz, 1 H), 2.13 (d, J = 1.1 Hz, 3 H), 2.07 (dqd, J = 10.0, 6.8, 2.4 Hz, 1 H), 1.87 (d, J = 1.2 Hz, 3 H), 1.25 (d, J = 7.6 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 173.6, 156.8, 124.1, 77.8, 74.3, 47.0, 43.9, 33.6, 27.7, 25.7, 20.9, 18.0, 16.1, 13.8, -4.5, -4.7; high resolution mass spectrum (ES) *m/z* 377.2127 [$(M+Na)^+$; calcd for $C_{19}H_{34}O_4SiNa$: 377.2124]

Alcohol (-)-65: A solution of enone (-)-**64** (6.0 g, 16.9 mmol) in toluene (170 mL) was cooled to -78 °C and treated with K-Selectride' (1.0 M in THF, 19.5 mL, 19.5 mmol). After 3 h, the mixture was added to a solution containing pH 7.0 buffer (100 mL), H_2O_2 (10 mL, 10% in

MeOH), and glacial AcOH (2 mL). The resulting solution was stirred for 45 min at ambient temperature. The aqueous layer was extracted with CH_2Cl_2 (4 x 200 mL) and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (15% ethyl acetate/hexanes, 1% AcOH) afforded (-)-**65** (3.09 g, 51%) as a colorless oil that solidified on standing. Recrystallization (hexanes) afforded colorless needles: mp 77.5-78.5 °C; $[\alpha]^{23}{}_{D}$ -21.1° (*c* 2.02, $CHCl_3$); IR ($CHCl_3$) 3620, 3400-3600 (br), 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (apparent dt, J = 8.6, 1.3 Hz, 1 H), 4.75 (br t, J = 9.1 Hz, 1 H), 4.60 (td, J = 9.9, 2.3 Hz, 1 H), 3.67 (t, J = 3.0 Hz, 1 H), 2.66 (qd, J = 7.5, 3.4 Hz, 1 H), 1.90 (dqd, 9.7, 6.8, 2.6 Hz, 1 H), 1.83 (ddd, J = 14.5, 9.9, 2.4 Hz, 1 H), 1.71 (d, J = 1.1 Hz, 3 H), 1.70 (d, J = 1.2 Hz, 3 H), 1.65 (br s, 1 H), 1.60 (ddd, J = 14.5, 10.1, 2.9 Hz, 1 H), 1.26 (d, J = 7.6 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 134.8, 127.7, 77.8, 74.2, 64.1, 43.7, 41.5, 34.6, 25.7, 25.6, 18.2, 17.9, 16.0, 13.7, -4.6, -4.8.

Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found: C, 63.92; H, 10.43.

TBS Ether (-)-66: A solution of alcohol (-)-65 (3.09 g, 8.67 mmol) and imidazole (1.92 g, 28.2 mmol) in DMF (44 mL) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl chloride (2.41 mg, 16.0 mmol). The resultant solution was stirred 12 h at ambient temperature, diluted with ether (75 mL), washed with H_2O (2 x 100 mL) and saturated brine (100 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (5% ethyl acetate/hexanes) afforded (-)-19 (3.55 g, 87%) as a colorless oil: $[\alpha]^{23}{}_{D}$ -20.6° (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.11 (apparent dt, J = 8.6, 1.3 Hz, 1 H), 4.71 (ddd, 10.4, 8.7, 2.2 Hz, 1 H), 5.55 (td, J = 10.4, 1.7 Hz, 1 H), 3.65

(t, J = 2.7 Hz, 1 H), 2.63 (qd, J = 7.6, 3.0 Hz, 1 H), 1.83 (dqd, 10.0, 6.8, 2.5 Hz, 1 H), 1.74 (ddd, J = 14.2, 10.5, 1.8 Hz, 1 H), 1.68 (d, J = 1.1 Hz, 3 H), 1.65 (d, J = 1.2 Hz, 3 H), 1.44 (ddd, J = 14.2, 10.6, 2.3 Hz, 1 H), 1.26 (d, J = 7.6 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 173.9, 131.6, 129.1, 77.4, 74.6, 65.2, 44.0, 42.8, 34.4, 25.9, 25.7, 25.6, 18.3, 18.1, 18.0, 16.4, 14.0, -4.3, -4.5, -4.8, -4.9; high resolution mass spectrum (EI) *m/z* 469.3156[$(M-H)^+$; calcd for $C_{25}H_{50}O_4Si_2$: 469.3156]

Fragment (-)-C: A solution of olefin (-)-**66** (570 mg, 1.20 mmol) in CH_2Cl_2 (20 mL) was cooled to -78 °C and treated with a stream of ozone and oxygen until the colorless solution became steel-blue in appearance. The reaction mixture was purged with a stream of argon for 40 min, followed by the cautious addition of triphenylphosphine (349 mg, 1.3 mmol). The cooling bath was removed, and the solution was stirred at ambient temperature for 1 h, concentrated, and chromatographed (20% ethyl acetate/hexanes) to afford (-)-**67** (508 mg, 94%) as a colorless oil that solidified upon standing at 5 °C. Recrystallization from hexanes afforded an analytical sample: mp 58-60 °C; $[\alpha]^{23}{}_{D}$ -55.5° (*c* 1.46, $CHCl_3$); IR ($CHCl_3$) 1730 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.67 (br s, 1 H), 4.52 (td, J = 10.5, 2.1 Hz, 1 H), 4.46 (dd, J = 10.5, 3.5 Hz, 1 H), 3.67 (t, J = 2.3 Hz, 1 H), 2.66 (qd, J = 7.6, 2.6 Hz, 1 H), 1.95-1.84 (m, 3 H), 1.77 (ddd, J = 14.1, 10.5, 2.1 Hz, 1 H), 1.27 (d, J = 7.6 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 173.1, 76.0, 74.7, 73.7, 44.2, 36.2, 34.1, 25.72, 25.66, 18.1, 17.9, 16.5, 14.0, -4.55, -4.63, -4.9, -5.2; high resolution mass spectrum (CI) *m/z* 445.2793

[$(M+H)^+$; calcd for $C_{22}H_{45}O_5Si_2$: 445.2806]

(+)-39 (Modified Negeshi Coupling): A 1.0 M solution of anhydrous $ZnCl_2$ (20 mL, 19.93 mmol) was added via syringe to a solution of alkyl iodide (+)-**A** (10.93 g, 19.93 mmol) in dry Et_2O (80 mL), and the resulting solution was degassed (2 freeze-pump thaw cycles). The solution was cooled to -78 °C, and *t*-BuLi (1.7 M in pentane, 35.2.0 mL, 59.8 mmol) was added via cannula over 12 min. The resultant solution was stirred 5 min further, evacuated and purged (1 X 0.1 Torr). The -78 °C bath was removed, and the reaction was stirred at ambient temperature for 1 h. The resulting cloudy suspension was transfered by cannula into a mixture of vinyl iodide (+)-**B** (8.98 g, 17.3 mmol; 9:1 Z/E) and $Pd(PPh_3)_4$ (1.0 g, 0.87 mmol). The reaction mixture was covered with aluminum foil, stirred overnight, and quenched via slow addition of the reaction mixture to water (200 mL). The mixture was diluted with Et_2O, and the layers were separated. The water layer was extracted (3 X Et_2O) and the combined organic layers were washed [saturated aqueous $NaHCO_3$, brine), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (gradient elution; 2% EtOAc/hexanes Æ 5% or to EtOAc/hexanes] gave a white wax that was recrystrallized from 75 mL of ethanol to afford (+)-**39** [9.3 g (two crops), 66% yield; 73% based on purity of vinyl iodide] as white needles: mp 81.0-81.5 °C; $[\alpha]^{23}{}_{,D}$ +28.6° (*c* 1.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) d 7.36 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 6.84 (d, *J* = 8.9 Hz, 2 H), 5.37 (s, 1 H), 5.00 (d, *J* = 10.2 Hz, 1 H), 4.36 (ABq, J_{AB} = 11.6 Hz, Dn_{AB} = 17.4 Hz, 2 H), 4.08 (dd, *J* = 11.2, 4.7 Hz, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.61 (dd, *J* = 7.1, 1.8 Hz, 1 H), 3.51 (dd, *J* = 9.9, 1.7 Hz, 1 H), 3.47 (apparent t, *J* = 11.0 Hz, 1 H), 3.46 (dd, *J* = 9.1, 5.0 Hz, 1 H), 3.38 (dd, *J* = 6.0, 4.8 Hz, 1 H), 3.19 (apparent t, *J* = 8.8 Hz, 1 H), 2.51 (ddq, *J* = 10.1, 6.5, 6.5 Hz, 1 H), 2.32

(apparent t, J = 12.2 Hz, 1 H), 2.08-2.02 (m, 1 H), 1.99-1.93 (m, 2 H), 1.88 (dqd, J = 7.1, 7.1, 1.8 Hz, 1 H), 1.67 (br d, J = 11.1 Hz, 1 H), 1.55 (d, J = 0.5 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.74 (d, J = 6.3 Hz, 3 H), 0.73 (d, J = 6.4 Hz, 3 H), 0.03 (s, 3 H), 0.013 (s, 3 H), 0.008 (s, 3 H), 0.003 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 159.0, 132.0, 131.5, 131.2, 131.1, 129.0, 127.3, 113.7, 113.5, 101.1, 83.4, 78.49, 78.46, 73.3, 72.6, 72.5, 55.3, 38.8, 38.2, 37.5, 35.6, 33.7, 30.8, 26.27, 26.25, 23.1, 18.42, 18.40, 17.0, 14.6, 12.6, 12.1, 10.9, -3.5, -3.7, -3.8, -3.9; high resolution mass spectrum (FAB, NBA) m/z 835.5315 [$(M+Na)^+$; calcd for $C_{47}H_{80}O_7Si_2Na$: 835.5341]. Anal. Calcd for $C_{47}H_{80}O_7Si_2$: C, 69.41; H, 9.91. Found: C, 69.52; H, 10.10.

Alcohol (+)-40 (Chemoselective Hydrolysis of PMB Ether): At 0 °C, a solution of PMB ether (+)-**39** (10.6 g, 12.95 mmol) in CH_2Cl_2 (124 mL) was treated with H_2O (6 mL) and DDQ (3.18 g, 13.99 mmol) and stirred for 3 h. The mixture was quenched with 20 mL saturated $NaHCO_3$, washed with H_2O (4 X) and seperated. The aqueous layer was then extracted with CH_2Cl_2 (2 X). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated from hexanes to provide an amorphous white solid. Recrystallization (250 mL EtOH) provided (+)-**40** (7.31 g) as white needles. The mother liquors were then treated with $NaBH_4$ (200 mg), and the reaction mixture concentrated, diluted with CH_2Cl_2, washed with aqueous saturated ammonium chloride and brine. The organic layer was dried over $NaSO_4$, decanted, concentrated and chromatographed (5% EtOAc/hexanes) to provided an additional 560 mg of (+)-**40** as a white solid (7.87g total, 88%): mp 99-100 °C; $[\alpha]^{23}{}_{D}$ +26.5° (c 0.95, $CHCl_3$); IR ($CHCl_3$) 3520 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 5.37 (s, 1 H), 5.01 (d, J =

10.1 Hz, 1 H), 4.09 (dd, J = 11.2, 4.7 Hz, 1 H), 3.79 (s, 3 H), 3.65 (dd, J = 10.4, 4.7 Hz, 1 H), 3.63 (dd, J = 7.0, 1.8 Hz, 1 H), 3.54-3.50 (m, 1 H), 3.51 (dd, J = 10.0, 2.0 Hz, 1 H), 3.47 (apparent t, J = 11.2 Hz, 1 H), 3.41 (dd, J = 6.6, 4.0 Hz, 1 H), 2.59 (ddq, J = 13.2, 6.7, 6.7 Hz, 1 H), 2.33 (apparent t, J = 12.2 Hz, 1 H), 2.24 (apparent t, J = 5.5 Hz, 1 H), 2.09-1.95 (m, 2 H), 1.89 (dqd, J = 7.0, 7.0, 1.7 Hz, 1 H), 1.84-1.77 (m, 1 H), 1.72 (br d, J = 11.0 Hz, 1 H), 1.58 (d, J = 0.8 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.910 (s, 9 H), 0.905 (s, 9 H), 0.75 (d, J = 7.1 Hz, 3 H), 0.74 (d, J = 7.1 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 133.0, 131.5, 130.5, 127.3, 113.4, 101.0, 83.3, 81.6, 78.4, 73.3, 65.4, 55.3, 38.5, 38.2, 37.6, 37.0, 33.7, 30.8, 26.17, 26.16, 23.2, 18.4, 18.3, 17.4, 15.7, 12.6, 12.1, 10.9, -3.57, -3.61, -3.66, -3.9; high resolution mass spectrum (CI, NH_3) *m/z* 693.4918 [$(M+H)^+$; calcd for $C_{39}H_{73}O_6Si_2$: 693.4945]. Anal. Calcd for $C_{39}H_{72}O_6Si_2$: C, 67.58; H, 10.47. Found: C, 67.20; H, 10.39.

Trityl protected anisylidene acetal (+)-87:

To a solution of alcohol (+)-**40** (8.16 g, 11.8 mmol) in pyridine (118 mL) were added trityl chloride (6.90 g, 24.8 mmol) and DMAP (3.02 g, 24.8 mmol). The mixture was then refluxed for 18 h, cooled to ambient temperature, and added to a solution of 1M citric acid (500 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL), washed with 1 M citric acid (2 X 100 mL) H_2O (100 mL) and saturated $NaHCO_3$ solution (100 mL). The organic solution was separated, dried ($NaSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (5% EtOAc/hexanes) provided (+)-**87** (10.38 g, 94%) as a white foam: $[\alpha]^{23}{}_{D}$ +16.7° (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 2980, 2880, 1620, 1255 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.62 (d, J

=8.69 Hz, 2 H), 7.60 (d, *J* =8.09 Hz, 6 H), 7.15 (dd, *J* =8.8, 6.6 Hz, 6 H), 7.04 (apparent t, *J* =7.4 Hz, 3 H), 6.84 (d, *J* =8.7, 2 H), 5.43 (s, 1 H), 5.06 (d, *J* =9.9 Hz, 1 H), 3.95 (dd, *J* =4.6, 11.0, 1 H), 3.77 (d, *J* =7.1 Hz, 1 H), 3.53 (m, 3 H), 3.48 (dd, *J* =5.2, 8.6, 1 H), 3.24 (s, 3 H), 3.00 (apparent t, *J* =8.9 Hz, 1 H), 2.72 (m, 1 H), 2.49 (apparent t, *J* =12.3 Hz, 1 H) 2.41 (m, 1 H), 2.19 (m, 1 H), 1.98 (m, 1 H), 1.92 (m, 2 H), 1.75 (apparent d, *J* =12.1 Hz, 1 H), 1.61 (s, 3 H), 1.23 (d, *J* =6.8 Hz, 3 H), 1.16 (d, *J* =7.0 Hz, 3 H), 1.14 (d, *J* =6.7 Hz, 3 H), 1.04 (s, 9 H), 0.98 (d, *J* =6.8 Hz, 3 H), 0.95 (s, 9 H), 0.42 (d, *J* =6.6 Hz, 3 H), 0.01 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.4, 145.2, 132.4, 129.2, 128.3, 128.0, 127.9, 127.1, 113.8, 101.8, 86.9, 83.5, 79.1 (2), 73.3, 66.6, 54.7, 40.7, 38.7, 37.9, 36.3, 33.9, 31.0, 26.5, 26.4, 23.2, 18.7, 18.5, 18.3, 14.5, 12.9, 11.9, 11.3, -3.3, -3.5, -3.6, -3.8; high resolution mass spectrum (FAB, NBA) *m/z* 959.6040 [$(M+Na)^+$; calcd for $C_{58}H_{86}O_6Si_2Na$: 959.6017].

Trityl protected alcohol (-)-88: To a 0 °C solution of trityl ether (+)-**87** (10.38 g, 11.1 mmol) in CH_2Cl_2 (111 mL) was added DIBAL-H (1M in Toluene, 33.3 mL, 33.3 mmol). The resulting solution was stirred for 4.5 h, quenched via dropwise addition of pH 7.0 buffer (20 mL), then diluted with CH_2Cl_2 (100 mL). The mixture was then added to 100 mL of saturated sodium potassium tartrate solution, extracted with CH_2Cl_2 (4 x 100mL), and separated. The organic layer was washed with H_2O (400 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (20% EtOAc/hexanes) provided (-)-**88** (9.5 g, 91%) as a white foam: $[\alpha]^{23}{}_{,D}$ - 30° (*c* 0.05, $CHCl_3$); IR ($CHCl_3$) 3500, 2940, 1640, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* =7.9, 1.4 Hz, 6 H), 7.26 (m, 8 H), 7.18 (m, 3 H), 6.87 (d, *J* =8.6 Hz, 2 H), 4.85 (d, *J* = 10.2 Hz, 1 H), 4.52 (d, *J* =10.5 Hz, 1

H), 4.49 (d, J =10.5 Hz, 1 H), 3.78 (s, 3 H), 3.73 (ddd, J =11.0, 5.2, 3.5 Hz), 3.57 (ddd, J =11.0, 5.5, 5.5 Hz, 1 H), 3.47 (dd, J =5.4, 3.4 Hz, 1 H), 3.38 (dd, J =6.3, 4.4 Hz, 1 H), 3.35 (apparent t, J =5.5 Hz, 1 H), 3.17 (dd, J =8.8, 5.4 Hz, 1 H), 2.74 (aqpparent t, J =8.8 Hz, 1 H) 2.42 (m, 1 H), 2.12 (m, 2 H), 1.93 (m, 2 H), 1.84 (m, 1 H), 1.48 (apparent d, J =11.0 Hz, 1 H), 1.40 (s, 3 H), 1.38 (m, 1 H), 1.03 (d, J =7.0 Hz, 3 H), 1.01 (d, J =6.9 Hz, 3 H), 0.96 (d, J =6.9 Hz, 3 H) 0.93 (s, 9 H), 0.86 (J =6.6 Hz, 3 H), 0.82 (s, 9 H), 0.70 (d, J =6.7 Hz, 3 H), 0.07 (s, 3 H), 0.02 (s, 3 H), -0.01 (s, 3 H), -0.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 144.6, 131.4, 131.0, 130.4, 129.3, 128.8 , 127.6, 126.7, 114.0, 86.3, 86.2, 78.2, 77.5, 75.2, 66.4, 65.5, 55.3, 40.2, 40.0, 37.5, 36.6, 35.7, 35.0, 26.2, 26.0, 22.9, 18.5, 18.2, 17.6, 15.6, 13.7, 13.5, 11.4, -3.4 (2), -3.9, -4.1; high resolution mass spectrum (FAB, NBA) m/z 957.5844 [$(M-2H+Na)^+$; calcd for $C_{58}H_{86}O_6Si_2Na$: 957.5861].

Trityl Protected Triene 90: To a 0 °C solution of alcohol (-)-**88** (2.65 g, 2.83 mmol) in CH_2Cl_2 (28 mL) were added Dess-Martin periodinane (1.31 g, 3.1 mmol) and $NaHCO_3$ (615 mg, 8.48 mmol). The resulting solution was stirred for 2.5 h and quenched with saturated NaS_2O_3 solution (15 mL) and saturated $NaHCO_3$ solution (15 mL). The mixture was then extracted with Et_2O (3 x) and separated. The organic solution was then washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The resulting white foam (2.54 g) was used without further purification [**89**]: IR ($CHCl_3$) 2960, 2850, 1720, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.87 (d, J = 2.5 Hz, 1 H), 7.54 (d, J = 7.5 Hz, 6 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.10 (m, 6 H), 6.99 (apparent t, 7.3 Hz, 3 H), 6.74 (d, J = 8.6 Hz, 2 H), 4.99 (d, J = 10.2 Hz, 1 H), 4.39 (d, J = 10.8 Hz, 1 H), 4.34 (d, J = 10.8 Hz, 1 H), 3.56 (dd,

J = 2.8, 5.8 Hz, 1 H), 3.53 (dd, J = 5.3, 5.2 Hz, 1 H), 3.50 (dd, J = 6.6, 4.3 Hz, 1 H), 3.41 (dd, J = 8.6, 5.4 Hz, 1 H), 3.24 (s, 3 H), 2.96 (apparent t, J = 8.9 Hz), 2.65 (m, 1 H), 2.51 (m, 1 H), 2.33 (apparent t, J = 12.4 Hz, 1 H), 1.95 (m, 1 H), 1.89 (m, 1 H), 1.64 (apparent d, J = 12.1 Hz, 1 H), 1.48 (s, 3 H), 1.18 (d, J = 6.9 Hz, 3 H), 1.07 (d, J = 4.2, 3 H), 1.05 (d, J = 4.6 Hz, 3 H), 0.97 (s, 9 H), 0.96 (s, 9 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.026 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 159.3, 144.6, 131.6, 131.5, 130.7, 129.5, 129.1 (3), 128.7, 128.0 (3), 127.1, 113.8, 86.3, 82.5, 78.2, 77.3, 74.4, 66.4, 55.2, 49.5, 40.3, 40.2, 36.6, 35.7, 34.7, 36.2 (3), 26.0 (3), 22.9, 18.5, 18.2, 17.6, 13.7, 13.2, 12.1, 11.4, -3.4 (2), -3.9, -4.1; high resolution mass spectrum (FAB, NBA) m/z 957.5861 [$(M+Na)^+$; calcd for $C_{58}H_{86}O_6Si_2Na$: 957.5963].

To a -78 °C solution of allyldiphenylphosphine (1.17 mL, 5.43 mmol) in THF (17 mL, degassed) was added 3.2 mL of t-butyllithium (1.7M in pentane, 5.43 mmol) and stirred for 5 min. The solution was then immersed into a 0 °C bath, stirred for 30 min and cooled to -78 °C. The solution was treated with Ti(i-OPr)$_4$ (1.61 mL, 5.43 mmol) and stirred for 30 min. A precooled (-78 °C) solution of aldehyde **89**(2.54 g, 2.72 mmol) in THF (10 mL) was added via cannula (rinse 1 X 2 mL) and stirred for 1 h, then warmed to 0 °C. Iodomethane (1.69 mL, 27.2 mmol) was added and the solution was warmed to ambient temperature and stirred for 16 h. The solution was quenched with pH 7.0 buffer (20 mL) and extracted with CH_2Cl_2 (3X) and Et_2O (3X). The combined organic layers were washed with saturated brine solution, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (2% EtOAc/hexanes) provided **90** (1.69 g, 62%, 2 steps, 8:1 mixture of diastereomers) as a white foam: IR ($CHCl_3$) 3060, 2940, 1600, 1450 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$,

major dastereomer) d 7.41 (d, J = 7.2 Hz, 6 H), 7.26 (m, 8 H), 7.18 (apparent t, J = 7.25 Hz, 3 H), 6.86 (d, J = 8.57, 2 H), 6.56 (ddd, J = 16.8, 10.7, 10.7 Hz, 1 H), 5.96 (apparent t, J = 11.0 Hz, 1 H), 5.52 (apparent t, J = 10.5 Hz, 1 H), 5.16 (d, J = 16.8 Hz, 1 H), 5.07 (d, J = 10.2 Hz, 1 H), 4.77 (d, J = 10.1 Hz, 1 H), 4.76 (d, J = 10.4 Hz, 1 H), 4.55 (d, J = 10.4 Hz, 1 H), 3.80 (s, 3 H), 3.37 (dd, J = 9.4, 4.5 Hz, 1 H), 3.35 (dd, J = 6.6, 4.3 Hz, 1 H), 3.23 (dd, J = 7.2, 3.7 Hz, 1 H), 3.13 (dd, J = 8.7, 5.5 Hz, 1 H), 2.97 (m, 1 H), 2.73 (apparent t, J = 8.9 Hz, 1 H), 2.35 (m, 1 H), 2.10 (m, 1 H), 1.90 (apparent t, J = 12.4 Hz, 1 H), 1.74 (m, 1 H), 1.69 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 159.1, 144.7, 134.5, 132.2, 131.7, 131.3, 130.6, 129.2, 129.1, 128.8, 127.6, 126.8, 117.6, 113.7, 86.3, 84.6, 78.2, 75.0, 66.5, 55.3, 40.5, 40.1, 35.9, 35.5, 35.4,35.2, 26.3, 26.0, 22.8, 18.6, 18.2, 17.7, 14.7, 14.1, 13.5, 10.5, -3.15, - 3.35, -3.97, -4.12; high resolution mass spectrum (FAB, NBA) m/z 981.6225 [$(M+Na)^+$; calcd for $C_{61}H_{90}O_5Si_2Na$: 981.6224].

Triene Alcohol 74: Anhydrous MeOH (151 mL) was added to a cold (0 °C) solution of chlorocatecholborane (2.31g, 14.5 mmol) in 4.5 mL of CH_2Cl_2 (3.2 M), and the resulting solution was added in 0.6 mL (1.94 mmol) aliquots at 10 min intervals to a 0.07 M solution of trityl ether **90** (1.86 g, 1.94 mmol, 8:1 dr) at 0 ° until TLC (20% EtOAc/hexanes) indicated ca. 90% reaction completion (total of 2.4 mL of rgt solution, 7.74 mmol), at which point the reaction was quenched via dropewise addition of 20 mL of saturated $NaHCO_3$. The resulting mixture was stirred for 15 min, diluted with 40 mL Et_2O, stirred an additional 30 min, and the layers were separated. The aqueous layer was extracted (3 X Et_2O), and the resulting organic layers were combined, washed (water and saturated brine solution), dried

($MgSO_4$), filtered, added to 10 g of SiO_2 and concentrated. Flash chromatography (gradient elution; 5% EtOAc/hexanes to 10% EtOAc/hexanes; 2nd column: 100% CH_2Cl_2; then 20% EtOAc/hexanes) provided **74** (1.20g, 86%, 8:1 dr) as a white foam and starting ether **90** (247 mg, 13%; 99% based on recovered starting material). $[\alpha]^{23}{}_{D}$ +32° (*c* 0.70, $CHCl_3$; 12:1 dr); IR ($CHCl_3$) 3500, 2950, 1620, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 7.27 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.61 (ddd, *J* = 16.8, 10.6, 10.6, 1 H), 6.05 (apparent t, *J* = 11.0 Hz, 1 H), 5.58 (apparent t, *J* = 10.6 Hz, 1 H), 5.23 (d, *J* = 16.8 Hz, 1 H), 5.12 (d, *J* = 10.3 Hz, 1 H), 4.98 (d, *J* = 10.2 Hz, 1 H), 4.57 (d, *J* = 10.6 Hz, 1 H), 4.45 (d, *J* = 10.5 Hz, 1 H), 3.80 (s, 3 H), 3.66 (ddd, *J* = 10.8, 4.8, 4.5, 1 H), 3.51 (ddd, *J* = 11.0, 5.7, 5.6 Hz, 1 H), 3.45 (dd, *J* = 4.7, 3.9 Hz, 1 H), 3.40 (dd, *J* = 6.9, 3.8 Hz, 1 H), .26 (dd, *J* = 7.3, 3.7 Hz, 1 H), 3.0 (m, 1 H), 2.56 (m, 1 H), 2.29 (apparent t, *J* = 5.52 Hz, 1 H), 2.06 (apparent t, *J* = 12.4 Hz, 1 H), 1.81 (m, 3 H), 1.65 (apparent d, *J* = 11.2 Hz, 1 H), 1.59 (s, 3 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H), 0.99 (d, *J* = 7.2 Hz, 3 H), 0.95 (s, 9 H), 0.92 (m, 12 H), 0.72 (d, *J* = 6.7 Hz, 3 H), 0.11 (s 9 H), 0.08 (s, 3 H), ; ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 159.1, 134.5, 132.8, 132.3, 131.2, 130.5, 129.2, 129.0, 117.5, 113.7, 84.6, 81.7, 77.1, 75.0, 65.3, 55.3, 40.1, 38.5, 36.8, 36.1, 35.4, 35.3, 26.7, 26.3, 26.2, 23.0, 18.7, 18.6, 18.3, 17.6, 15.8, 14.6, 10.6, -3.2, -3.4, -3.6, -3.9; high resolution mass spectrum (FAB, NBA) *m/z* 739.5129 [$(M+Na)^+$; calcd for $C_{42}H_{76}O_5Si_2Na$: 739.5156].

Phosphonium Salt 75: A solution of iodine (1.07 g, 4.24 mmol) in 10 mL of Et_2O was added dropewise to a vigorously stirred solution of alcohol (+)-**74** (1.41 g, 1.97 mmol; 8:1 mix of *cis/trans* diene isomers), PPh_3 (1.37g, 5.22

mmol) and imidazole (342 mg, 5.02 mmol) in benzene/ether (1:1, 40 mL) at 0 °C. The resultant cannary yellow suspention was stirred 30 min at 0 °C and poured into 150 mL of 1:1 water/hexanes. The layers were separated and the aqueous layer was extracted with hexanes. The combined organic layers were washed with saturated aqueous sodium metabisulfite (2 X 50 mL), water (1 X 50 mL) and brine (100 mL). The clear, colorless organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting white slurry was loaded onto a plug of SiO_2 with a minimal amount of CH_2Cl_2 and rapidly eluted off the column (0.05% Et_3N/2% Et_2O/hexanes) to afford the corresponding iodide as colorless oil (8:1 ds mixture of diene isomers; contaminated with ca. 20% PPh_4) which was taken on to the next step without further purification: ^1H NMR (500 MHz, C_6D_6, major diene isomer) δ 7.51 (m, 6 H), 7.43 (d, *J* = 8.6 Hz, 2 H), 7.18 (m, 9 H), 6.97 (d, *J* =8.6 Hz, 2 H), 6.84 (ddd, *J* =16.8, 10.8, 10.8 Hz, 1 H), 6.23 (apparent t, *J* =10.8 Hz, 1 H), 5.84 (apparent t, *J* =10.5 Hz, 1 H), 5.33 (dd, *J* =16.8, 1.9 Hz, 1 H), 5.27 (d, *J* =10.4, 1 H), 5.23 (d, *J* =10.2 Hz), 4.74 (d, *J* =10.7 Hz, 1 H), 4.66 (d, *J* =10.7 Hz, 1 H), 3.76 (apparent t, *J* =4.4 Hz, 1 H), 3.58 (dd, *J* =6.6, 4.0 Hz, 1 H), 3.48 (m, 2 H), 3.46 (s, 3 H), 3.24 (m, 1 H), 3.17 (dd, *J* =9.6, 8.0 Hz, 1 H), 2.80 (m, 1 H), 2.44 (apparent t, *J* =12.3 Hz, 1 H), 2.17 (m, 1 H), 2.10 (m, 1 H), 2.02 (m, 1 H), 1.78 (s, 3 H), 1.38 (d, *J* =6.9 Hz, 3 H), 1.27 (d, *J* =6.8 Hz, 3 H), 1.20 (s, 9 H), 1.18 (m, 6 H), 1.10 (s, 9 H), 1.06 (d, *J* =6.7 Hz, 3 H), 0.33 (s, 3 H), 0.31 (s, 3 H), 0.24 (s, 3 H), 0.23 (s, 3 H).

To a solution of above Iodide in benzene/toluene (7:3, 5.0 mL) was added diisopropylethylamine (0.2 mL, 1.14 mmol) and triphenylphosphine (2.5 g, 9.53 mmol). The resulting solution was loaded into a 20 mL polyethylene syringe and capped in such a way as to eliminate any trapped air (3 X 1.0 mL rinse of 7:3 benzene/toluene solution). The

syringe was loaded into a high pressure apparatus and subjected to a pressure of 12.8 Kbar. After 14 days, the reaction mixture was concentrated and chromatographed (gradient elution, 20% EtOAc/hexanes to 50% EtOAc/hexanes, then 20% MeCN/CH_2Cl_2) to provide **75** as a light yellow solid [1.68 g, 78% yield from alcohol **46**; 8:1 dr]: $[\alpha]^{23}{}_{,D}$ + 22° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2940, 1610, 1580, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, Major isomer) δ 7.75 (m, 15 H) 7.27 (d, *J* = 8.6 Hz, 2 H) 6.86 (d, *J* = 8.6 Hz, 2 H), 6.54 (ddd, *J* = 16.8, 10.6, 10.6 Hz, 1 H), 5.89 (apparent t, *J* = 11.0 Hz, 1 H), 5.50 (apparent t, *J* = 10.5 Hz, 1 H), 5.30 (d, *J* = 10.6 Hz, 1 H), 5.12 (d, *J* = 16.8 Hz, 1 H), 5.08 (d, *J* = 10.2 Hz, 1 H), 4.56 (d, *J* = 10.4 Hz, 1 H), 4.45 (d, *J* = 10.4 Hz, 1 H), 3.78 (s, 3 H), 3.70 (m, 1 H), 3.69 (dd, *J* = 6.7, 4.6 Hz, 1 H), 3.42 (dd, *J* = 5.3, 3.1 Hz, 1 H), 3.23 (dd, *J* = 7.9, 3.2 Hz, 1 H), 3.19 (m, 1 H), 2.97 (m, 1 H), 2.41 (m, 1 H), 2.03 (m, 1 H), 1.94 (apparent t, *J* = 12.2 Hz, 1 H), 1.84 (m, 2 H), 1.57 (m, 1 H), 1.54 (s, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H),).89 (m, 21 H), 0.69 (d, *J* = 6.9 Hz, 3 H), 0.66 (d, *J* = 6.7 Hz, 3 H), 0.095 (s, 3 H), 0.08 (s, 3 H), 0.04 (s, 3 H), - 0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 135.3, 135.2, 134.2, 133.5, 133.4, 132.5, 132.3, 131.0, 130.9, 130.7, 130.6, 130.4, 129.1, 128.8, 128.2, 118.6, 118.0, 117.6, 113.7, 84.6, 80.0, 79.9, 76.8, 75.1, 55.3, 39.8, 35.8, 35.5, 35.3, 35.2, 26.2, 26.1 (2), 26.0, 22.6, 18.6, 18.5, 18.2, 17.4, 16.9, 15.0, 10.5, -3.3, -3.4 (2), -4.0; high resolution mass spectrum (FAB, NBA) *m/z* 961.6134[$(M-I)^+$; calcd for $C_{60}H_{90}O_4PSi_2$: 961.6115].

Tetraene 58 (Wittig Coupling): Phosphonium salt **75** (1.20g, 1.10 mmol; 8:1 ratio of diene isomers), was azeotropically dried with benzene (3 X 1.5 mL) using a double manifold and further dried by heating to 50 °C under vacuum (0.2 torr) for 12 h. The salt was dissolved in 6 mL

of freshly distilled THF, sparged with argon for 15 min, and cooled to -20 °C. The resultant solution was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 1.04 mL), stirred 15 min, warmed to 0 °C, stirred 30 min, and re-chilled to -24 °C. To this orange/red solution was transferred via cannula a degassed solution of aldehyde (-)-**67** (508 mg, 1.14 mmol) in THF (3 mL + 1 X 0.5 mL rinse) over 7 min. The orange solution was allowed to slowly warm to -8 °C over 3.25 h. The resulting light yellow solution was quenched with saturated NH_4Cl, diluted with Et_2O and H_2O. The layers were separated, and the aqueous layer was extracted (3 X Et_2O). The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed (gradient elution; 2% EtOAc/hexanes or 50% to EtOAc/hexanes; then 40% CH_3CN/CH_2Cl_2) to afford *cis* isomer **58** (767 mg, 65%; white foam, 8:1 ratio of diene isomers), *transi* isomer **58** (50 mg, 4%; clear oil; 8:1 ratio of diene isomers), and phosphonium salt **75** (399 mg, 33%; 8:1 ratio of diene isomers). [enant-(+)-**58** $[\alpha]^{23}{}_{D}$ -32° (*c* 0.23, $CHCl_3$)]; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major diene isomer) δ 7.25 (d, *J* = 9.0 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.57 (ddd, *J* = 16.7, 10.6, 10.6 Hz, 1 H), 6.00 (apparent t, *J* = 11.0 Hz, 1 H), 5.55 (apparent t, *J* = 10.5 Hz, 1 H), 5.26 (dd, *J* = 11.1, 7.9 Hz, 1 H), 5.19 (dd, *J* = 15.4, 1.4 Hz, 1 H), 5.18 (apparent t *J* = 10.1 Hz, 1 H), 5.10 (d, *J* = 10.2 Hz, 1 H), 5.01 (d, *J* = 10.0 Hz, 1 H), 4.75 (apparent t, *J* = 9.2 Hz, 1 H), 4.50 (ddd, *J* = 10.5, 1.3, 1.3 Hz, 1 H), 4.50 (ABq, J_{AB} = 10.6 Hz, Δ_{AB} = 42.6 Hz, 2 H), 3.78 (s, 3 H), 3.60 (apparent t, *J* = 2.4 Hz, 1 H), 3.42 (dd, *J* = 5.1, 3.7 Hz, 1 H), 3.23 (dd, *J* = 7.5, 3.7 Hz, 1 H), 3.20 (apparent t, *J* = 5.4 Hz, 1 H), 3.01-2.94 (m, 1 H), 2.60 (qd, *J* = 7.7, 2.6 Hz, 1 H), 2.62-2.55 (m, 1 H), 2.45-2.38 (m, 1 H), 1.98 (apparent t, *J* = 12.3 Hz, 1 H), 1.84-1.67 (m, 3 H), 1.63 (br d, *J* = 13.2 Hz, 1 H), 1.52 (s, 3 H), 1.55-1.48 (m, 1 H), 1.20 (d, *J* =

7.6 Hz, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.93 (apparent d, J = 6.7 Hz, 6 H), 0.93 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.85 (s, 9 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.69 (d, J = 6.7 Hz, 3 H), 0.085 (s, 3 H), 0.079 (s, 3 H), 0.051 (s, 3 H), 0.046 (s, 3 H), 0.042 (s, 3 H), 0.029 (s, 3 H), 0.028 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 159.1, 134.4, 133.4, 132.4, 132.2, 131.9, 131.3, 131.2, 129.11, 129.09, 117.6, 113.7, 84.6, 80.5, 76.9, 75.0, 74.9, 64.6, 55.3, 44.1, 42.7, 40.1, 37.5, 36.0, 35.44, 35.37, 35.2, 34.2, 26.31, 26.28, 25.9, 25.7, 23.0, 18.7, 18.6, 18.4, 18.1, 18.0, 17.1, 16.5, 16.4, 14.9, 14.1, 10.5, -3.0, -3.2, -3.3, -4.3, -4.4, -4.5, -4.8, -4.9; high resolution mass spectrum (FAB, NBA) *m/z* 1149.7836 [$(M+Na)^+$; calcd for $C_{64}H_{118}O_8Si_4Na$: 1149.7802].

Alcohol (+)-59: At 0 °C, a solution of PMB ether **58** (1.12 g, 0.993 mmol, 8:1 mixture of *cis/trans* diene isomers) in CH_2Cl_2 (10 mL) was treated with H_2O (0.5 mL) and DDQ (270 mg, 1.19 mmol). The mixture was stirred for 10 min at 0 °C, warmed to rt and stirred an additional 5 min. The mixture was quenched with 50 mL saturated $NaHCO_3$, diluted with CH_2Cl_2 (300 mL), and washed with H_2O (500 mL) and saturated brine solution (500 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (gradient elution; 4%EtOAc to 20% EtOAc/hexanes) provided (+)-**59** (822 mg, 82%) as a white foam: [enant-(+)-**33** $[\alpha]^{23}{}_{D}$ -20° (*c* 0.34, $CHCl_3$)]; IR (film, NaCl) 3500 (br), 1740cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (ddd, J = 16.8, 10.9, 10.9 Hz, 1 H), 6.13 (apparent t, J = 11.0 Hz, 1 H), 5.32 (apparent t, J = 10.5 Hz, 1 H), 5.28 (dd, J = 11.1, 7.9 Hz, 1 H), 5.24-5.21 (m, 1 H), 5.19 (apparent t, J = 10.3 Hz, 1 H), 5.14 (d, J = 10.2 Hz, 1 H), 5.06 (d, J = 10.0 Hz, 1 H), 4.76 (apparent t, J = 9.3 Hz, 1 H), 4.50 (apparent t, J = 9.9 Hz, 1 H), 3.62 (apparent t, J

= 2.4 Hz, 1 H), 3.60 (dd, J = 5.5, 3.4 Hz, 1 H), 3.32 (br d, J = 5.3 Hz, 1 H), 3.24 (apparent t, J = 5.1 Hz, 1 H), 2.79 (ddq, J = 9.9, 6.7, 6.7 Hz, 1 H), 2.60 (qd, J = 7.6, 2.7 Hz, 1 H), 2.63-2.57 (m, 1 H), 2.50-2.45 (m, 1 H), 2.16 (apparent t, J = 12.3 Hz, 1 H), 1.90-1.77 (m, 3 H), 1.75-1.69 (m, 2 H), 1.57 (s, 3 H), 1.60-1.50 (m, 1 H), 1.20 (d, J = 7.6 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.95-0.93 (m, 6 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.89-0.84 (m, 3 H), 0.87 (s, 9 H), 0.85 (s, 9 H), 0.73 (d, J = 6.8 Hz, 3 H), 0.07 (apparent s, 6 H), 0.052 (s, 3 H), 0.051 (s, 3 H), 0.04 (apparent s, 6 H), 0.03 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 173.3, 134.7, 133.5, 132.5, 132.1, 132.0, 131.5, 131.0, 118.4, 80.5, 78.8, 76.4, 74.9, 64.7, 44.1, 42.7, 38.0, 37.4, 36.3, 36.1, 35.2, 35.1, 34.2, 26.3, 26.2, 25.9, 25.7, 23.2, 18.5, 18.1, 18.0, 17.3, 17.2, 16.4, 16.1, 14.1, 13.7, 9.4, -3.0, -3.3, -3.6, -4.34, -4.36, -4.5, -4.8; high resolution mass spectrum (FAB, NBA) *m/z* 1029.7273 [$(M+Na)^+$; calcd for $C_{56}H_{110}O_7Si_4Na$: 1029.7226; **DDQ Adduct 32:** $[\alpha]^{23}{}_{,D}$ +47° (c 1.2, $CHCl_3$)]; IR ($CHCl_9$) 3225, 2900, 1710, 1580, 1070 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, 1:1 mixture of C21 diastereomers) δ 5.60 (m, 2 H), 5.26 (m, 2 H), 5.15 (m, 2 H) 4.75 (apparent t, J = 10.5 Hz, 1 H), 4.43 (dd, J = 11.6, 1.0 Hz, 1 H), 3.47 (m, 2 H), 3.04 (2, 1 H), 2.92 (m, 1 H), 2.80 (m, 1 H), 2.73 (m, 1 H), 2.66 (m, 1 H), 2.44 (apparent d, J = 9.6 Hz, 1 H), 2.25 (m, 2 H), 2.12 (dd, J = 17.1, 5.4 Hz, 1 H), 1.86 (m, 7 H), 1.76 (m, 1 H), 1.70 (apparent t, J = 12.6 Hz, 1 H), 1.24 (d, J = 6.8 Hz, 3 H), 1.21 (d, J = 6.6 Hz, 3 H), 1.15 (d, J = 7.6 Hz, 3 H), 1.13 (s, 9 H), 1.08 (s, 9 H), 1.06 (s, 9 H), 1.01 (d, J = 6.7 Hz, 3 H), 0.94 (s, 9 H), 0.94 (s, 9 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.40 (d, J = 6.6 Hz, 3 H), 0.34 (s, 3 H), 0.30 (s, 3 H), 0.27 (s, 3 H), 0.26 (s, 3 H), 0.21 (s, 6 H), -0.01 (s, 3 H), -0.04 (s, 3 H); high

resolution mass spectrum (FAB, NBA) m/z 1255.6598 [$(M+Na)^+$; calcd for $C_{64}H_{110}Cl_2N_2O_9Si_4Na$: 1255.6563].

Carbamate (-)-60. A solution of alcohol (+)-**59** (822 mg, 0.816 mmol) in CH_2Cl_2 (8.2 mL) was treated with $Cl_3CCON{=}C{=}O$ (980 mL, 0.979 mmol) at room temperature for 30 min. Solution was loaded directly onto neutral Al_2O_3 (1.5 X 4" plug). After 4 h, the material was flushed from the Al_2O_3 (EtOAc, 500 mL), concentrated, and purified by flash chromatography (10% ethyl acetate/hexanes) providing 786 mg (+)-**60** (92%) as a white foam: [enant (+)-**60** $[\alpha]^{23}{}_{,D}$ -37° (c 0.19, $CHCl_3$)]; IR (film, NaCl) 3510, 3360 (br), 3180, 1730 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 6.58 (dddd, J = 16.8, 10.6, 10.6, 0.7 Hz, 1 H), 6.01 (apparent t, J = 11.0 Hz, 1 H), 5.36 (apparent t, J = 10.4 Hz, 1 H), 5.27 (dd, J = 11.1, 7.9 Hz, 1 H), 5.22-5.16 (m, 2 H), 5.12 (d, J = 10.1 Hz, 1 H), 5.03 (d, J = 10.0 Hz, 1 H), 4.76 (apparent t, J = 9.2 Hz, 1 H), 4.71 (apparent t, J = 6.1 Hz, 1 H), 4.50 (ddd, J = 10.5, 10.5, 1.3 Hz, 1 H), 4.44 (br s, 2 H), 3.62 (apparent t, J = 2.4 Hz, 1 H), 3.42 (apparent t, J = 4.5 Hz, 1 H), 3.22 (apparent t, J = 5.3 Hz, 1 H), 2.98 (ddq, J = 10.1, 6.6, 6.6 Hz, 1 H), 2.60 (qd, J = 7.6, 2.7 Hz, 1 H), 2.63-2.55 (m, 1 H), 2.48-2.41 (m, 1 H), 2.09 (apparent t, J = 12.4 Hz, 1 H), 1.93-1.88 (m, 1 H), 1.87-1.77 (m, 2 H), 1.71 (ddd, J = 14.1, 10.8, 1.6 Hz, 1 H), 1.67 (br d, J = 13.7 Hz, 1 H), 1.56 (apparent s, 3 H), 1.55-1.50 (m, 1 H), 1.21 (d, J = 7.6 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 7.5 Hz, 3 H), 0.918 (d, J = 6.8 Hz, 3 H), 0.915 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.853 (d, J = 6.4 Hz, 3 H), 0.847 (s, 9 H), 0.70 (d, J = 6.8 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.053 (s, 3 H), 0.051 (s, 3 H), 0.040 (s, 3 H), 0.037 (s, 3 H), 0.03 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 173.3, 156.9, 133.6, 133.5, 132.4, 132.1, 131.9, 131.4, 129.8, 118.0,

80.5, 78.9, 74.9, 64.6, 44.2, 42.7, 37.8, 37.4, 36.0, 35.3, 35.2, 34.5, 34.2, 26.3, 26.2, 25.9, 25.7, 23.0, 18.5, 18.4, 18.1, 18.0, 17.5, 17.1, 16.44, 16.38, 14.1, 13.7, 10.1, -3.0, -3.4, -3.6, -4.4, -4.5, -4.8; high resolution mass spectrum (FAB, NBA) *m/z* 1072.7264 [$(M+Na)^+$; calcd for $C_{57}H_{111}NO_8Si_4Na$: 1072.7283].

(+)-Discodermolide [1]. Carbamate (+)-60 (202 mg, 0.191 mmol) was dissolved in MeOH (70 mL) and stirred for 15 min at room temperature. Aqueous hydrochloric acid (3N, 40 mL) was added in 2-4 mL portions over 4 hours at a rate which minimized precipitation (ca. 10 to 15 min intervals). An additional 20 mL of 3 N aq HCl was added over 1 h at 15 min intervals, and the sides of the flask/stir bar were rinsed with 8 mL of MeOH. After 8 h, an additional 20 mL of 3 N aq HCl was added in one portion, and the resulting solution was stirred for 2 h at rt, diluted with 350 mL of water and poured into 400 mL of EtOAc. The resulting layers were separated, and the aqueous layer was saturated with NaCl and extracted (3 X EtOAc). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 X 100 mL) and saturated brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (gradient elution; 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave **1** (107 mg, 93% yield) as a white amorphous solid. X-ray quality crystals were obtained by dissolving the amorphous solid in acetonitrile (0.1 M) at rt and allowing the solution to stand for several hours at rt: mp 108-111 °; $[\alpha]^{23}{}_{D}$ +16° (*c* 0.033, MeOH); IR ($CHCl_3$) 3690, 3620, 3540, 3430, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (dddd, *J* = 16.8, 8.4, 8.4, 0.8 Hz, 1 H), 6.02 (apparent t, *J* = 11.1 Hz, 1 H), 5.51 (dd, *J* = 11.2, 7.9 Hz, 1 H), 5.42 (ddd, *J* = 10.6, 10.6, 0.6 Hz, 1 H), 5.34 (apparent t, *J* = 10.4 Hz, 1 H), 5.20 (dd, *J* = 16.9, 1.9 Hz, 1 H), 5.16 (d, *J* = 10.0 Hz, 1 H), 5.11 (d, *J* = 10.1 Hz, 1 H), 4.77-4.69 (m, 1 H), 4.70 (dd, *J* = 7.3, 4.2 Hz, 1 H), 4.60 (ddd, *J* = 10.0, 10.0, 2.4 Hz, 1 H), 4.56 (br s, 2 H), 3.73 (m, 1 H), 3.28

(m, 1 H), 3.18 (dd, J = 6.8, 4.8 Hz, 1 H), 2.98 (ddq, J = 10.1, 6.9, 6.9 Hz, 1 H), 2.78 (ddq, J = 9.8, 6.8, 6.8 Hz, 1 H), 2.66 (qd, J = 7.3, 4.6 Hz, 1 H), 2.60-2.55 (m, 1 H), 2.10-1.80 (m, 10 H), 1.69 (ddd, J = 14.4, 10.3, 3.1 Hz, 1 H), 1.64 (d, J = 1.3 Hz, 3 H), 1.30 (d, J = 7.4 Hz, 3 H), 1.06 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 173.6, 157.0, 134.4, 133.7, 133.4, 132.9, 132.2, 129.9, 129.8, 117.9, 79.1, 78.9, 77.2, 75.7, 73.2, 64.4, 43.1, 41.0, 37.4, 36.1, 36.0, 35.8, 35.3, 34.8, 33.1, 23.3, 18.4, 17.4, 15.6, 15.5, 13.7, 12.5, 9.0; high resolution mass spectrum (FAB, NBA) m/z 616.3840 [$(M+Na)^+$; calcd for $C_{33}H_{55}NO_8Na$: 616.3826].

Example 76: Mesylate 1201.

To a solution of alcohol **1200** (0.032 mmol) in CH_2Cl_2 (1mL) was added triethylamine (7μL) and methanesulfonylchlroride (4μL). After stirring for 1 hour 1 mL of sodium bicarbonate solution was added and the mixture was extracted (3x, CH_2Cl_2), dried (MgSO4), filtered, and concentrated. Purification was performed by flash chromatography (25% EtOAc/Hexanes) to provide 29 mg of mesylate **1201** (91%) as a clear oil.

Example 77: Isopropyl adduct 1206.

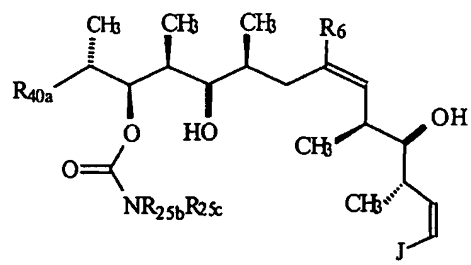
To a 0° C ethereal solution of mesylate **1201** (0.0269 mmol in 3 mL) was added LiAlH4. The mixture was stirred for 45 min. and quenched with Rochelle's solution (5mL). The mixture was stirred for 30 min and extracted with Et2O (2x) and CH_2Cl_2 (2x). The combined organic extracts were washed (Brine), dried (MgSO4), filtered, and concentrated. Flash chromatography (10% EtOAc/Hexanes) provided 19 mg (80%) of the isopropyl adduct **1206** as a yellow oil.

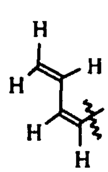
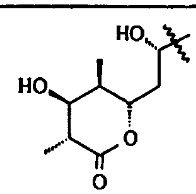
Example 78: Propyl adduct 1202.

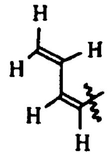
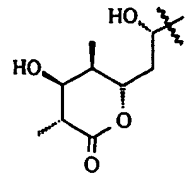
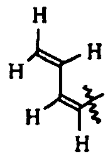
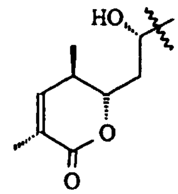
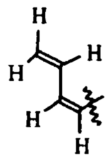
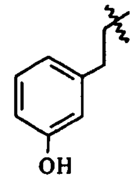
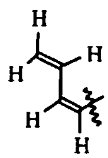
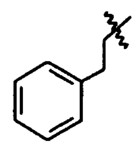
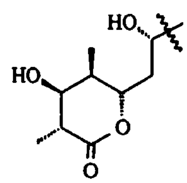
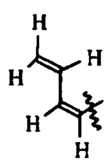
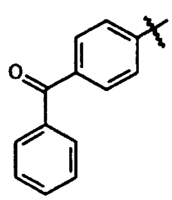
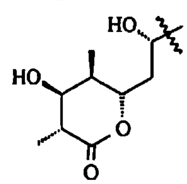
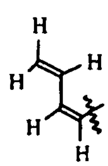
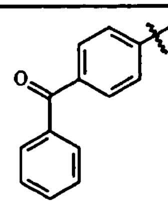
To a solution of CuI in THF (0.1 M) was added propylmagnesium bromide. The solution was stirred for 1 h and a solution of mesylate **1201** added via cannula (THF). The reaction was stirred for 3 hours and quenched with sodium bicarbonate solution. The mixture was extracted with Et2O (2x) and CH_2Cl_2 (2x). The combined organic extracts were washed (sodium bicarbonate, brine), dried (MgSO4), filtered, and concentrated. Flash chromatography was performed (10% EtOAc/Hexanes) to provide the propyl adduct **1202**.

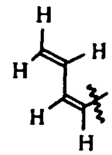
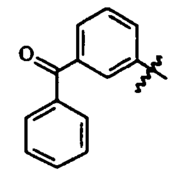
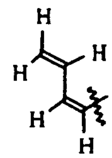
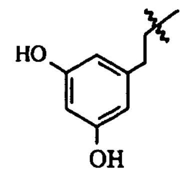
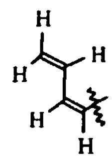
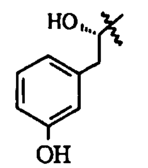
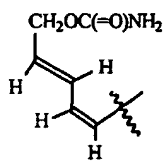
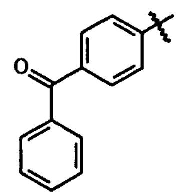
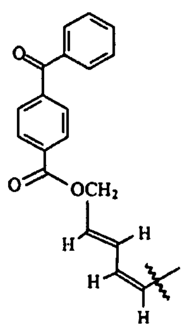
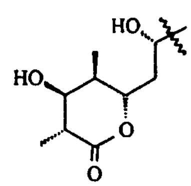
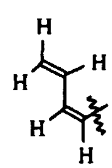
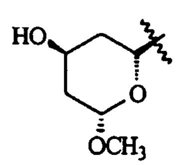
The present invention can be further understood by reference to Table III, which provides *in vitro* Tubulin Polymerization Assay and human A459 cell line results for compounds of the present invention.

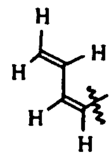
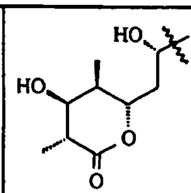
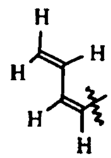
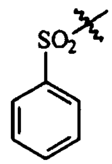
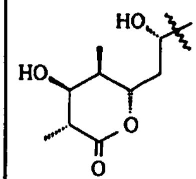
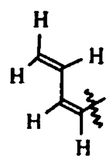
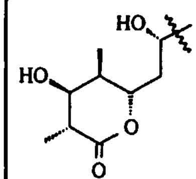
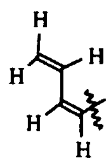
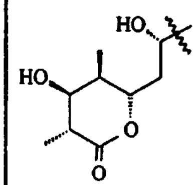
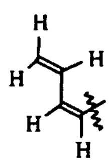
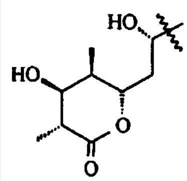
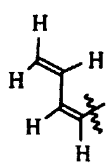
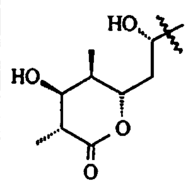
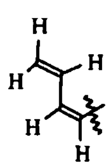
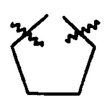
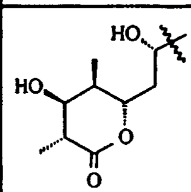
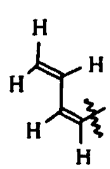
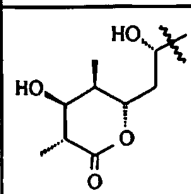
Table III

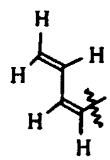
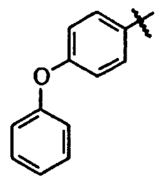
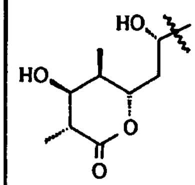
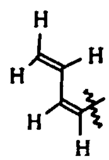
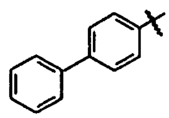
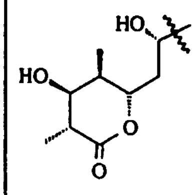
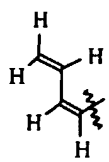
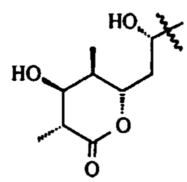


R_{40a}	R_{25b}; R_{25c}	R_6	J	Tubulin Polymerization	A549
	H;H	CH_3		100	3.8

	H;H	H		100	7.8
	H;H	CH_3		100	1.8
	H;H	CH_3		30	54
	H;H	CH_3		20	167
CH_3	H;H	CH_3		40	>5,000
		CH_3		70	0.7
	H;H	CH_3		0	92

	H;H	CH_3		10	259
	H;H	CH_3			
	H;H	CH_3			
	H;H	CH_3			
	H;H	CH_3			
	H;H	CH_3			

		CH_3			
		CH_3			
	CH_3	CH_3			
	$CH(CH_3)_2$	CH_3			
	$CH_2CH_2CH_3$	CH_3			
	$-CH(CH_3)-CH_2CH_3$	CH_3			
		CH_3			
		CH_3			

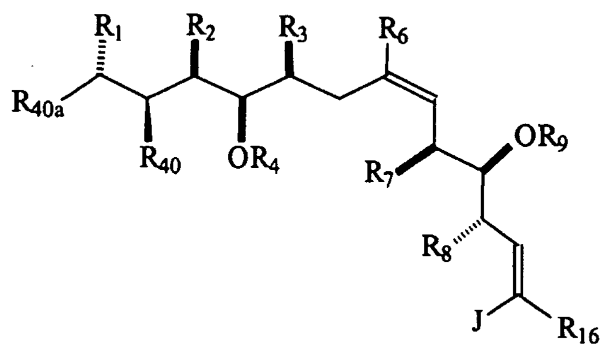
		CH_3			
		CH_3			
	3-fluorene	CH_3			

Those skilled in the art will appreciate that numerous changes and modifications may be made to the preferred embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all equivalent variations as fall within the true spirit and scope of the invention. All references cited herein are hereby incorporated by reference in their entireties.

CLAIMS

What is claimed is:

1. A compound of formula I-a:



I-a

wherein:

R_1, R_2, R_3, R_6, R_7, R_8, and R_{16} are independently selected from hydrogen and C_1-C_{10} alkyl;

R_4 and R_9 are selected from hydrogen and an acid labile protecting group;

R_{40} is $-OC(=R_{25a})NR_{25b}R_{25c}$;

R_{25a} is selected from O, S, NR_{25e};

R_{25e} is selected from hydrogen and C_{1-6} alkyl;

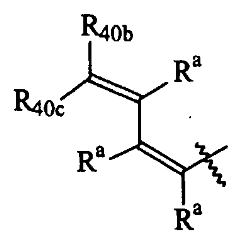
R_{25b} and R_{25c} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, OR^c, $C(=O)R^b$, $S(O)_pR^b$, $(CH_2)_rC_3$-C_{12} carbocycle, and $(CH_2)_r$heterocycle, wherein the alkyl, alkenyl, alkynyl, carbocycle, and heterocycle are substituted with 0-5 R_{25d};

alternatively, R_{25b} and R_{25c} may join with the nitrogen to which they are attached to form a 5- or 6-membered heterocycle containing 0-3 additional heteroatoms

selected from O, S, and N, wherein the heterocycle is substituted with 0-5 R_{25d};

R_{25d}, at each occurrence, is selected from F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, OH, NR^aR^a, OR^c, $C(=O)R^b$, CO_2R^c, $OC(=O)R^b$, $NR^aC(=O)R^b$, $C(=O)NR^aR^a$, $OC(=O)NR^aR^a$, $NR^aC(=O)OR^b$, $NR^aS(=O)_2R^b$, $S(=O)_2NR^aR^a$, $NR^aC(=S)R^b$, $C(=S)NR^aR^a$, $NR^aC(=O)NR^aR^a$, $NR^aC(=S)NR^aR^a$, $CH=NOR^c$, $CH=NR^a$, $CH=NNR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$, $S(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^g$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^g$, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, phenoxy, benzoyl, C_3-C_{12} carbocycle, and heterocycle, wherein phenoxy, benzoyl, carbocycle and heterocycle are substituted with 0-5 R^e;

R_{40a} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, $(CH_2)_r$heterocycle, wherein R_{40a} is substituted with 0-5 R^e, or alternatively, R_{40a} has the formula:



wherein R_{40b} and R_{40c} are independently selected from hydrogen, F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, $(CH_2)_rNR^aR^a$, $(CH_2)_rOR^c$, $(CH_2)_rC(=O)R^b$, $(CH_2)_rCO_2R^c$, $(CH_2)_rOC(=O)R^b$, $(CH_2)_rNR^aC(=O)R^b$, $(CH_2)_rC(=O)NR^aR^a$, $(CH_2)_rOC(=O)NR^aR^a$, $(CH_2)_rNR^aC(=O)OR^b$, $(CH_2)_rNR^aS(=O)_2R^b$, $(CH_2)_rS(=O)_2NR^aR^a$, $(CH_2)_rNR^aC(=S)R^b$, $(CH_2)_rC(=S)NR^aR^a$, $(CH_2)_rNR^aC(=O)NR^aR^a$, $(CH_2)_rNR^aC(=S)NR^aR^a$, $(CH_2)_rCH=NOR^c$, $(CH_2)_rCH=NR^a$, $(CH_2)_rCH=NNR^aR^a$, $(CH_2)_rC(=NR^a)NR^aR^a$, $(CH_2)_rNR^aC(=NR^a)NR^aR^a$, $(CH_2)_rS(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^g$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^g$, phenoxy, benzoyl, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $(CH_2)_rC_3$-C_{10} carbocycle and $(CH_2)_r$heterocycle, wherein alkyl, carbocycle and heterocycle are substituted with 0-5

R^e;

R^a is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, and $(CH_2)_r$heterocycle, wherein R^a is substituted with 0-5 R^e;

R^b is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_rC_{3-6}$ cycloalkyl, $(CH_2)_r$phenyl, and $(CH_2)_r$heterocycle, wherein R^b is substituted with 0-5 R^e;

R^c is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and $(CH_2)_r$phenyl, wherein R^c is substituted with 0-5 R^e;

R^d is independently the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;

R^e is independently selected from F, Cl, Br, I, OR^f, NO_2, CN, CF_3, CF_2CF_3, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, CO_2R^f, $OC(=O)R^f$, $C(=O)R^f$, $NHC(=O)R^f$, $OC(=O)NR^fR^f$, NR^fR^f, $C(=NR^f)NR^fR^f$, $NR^fC(=O)NR^fR^f$, $(CH_2)_r$phenyl, phenoxy, benzoyl, $(CH_2)_r$heterocycle, and =O;

R^f is independently selected from hydrogen and C_{1-6} alkyl;

R^g is independently the residue of an amino acid after the hydrogen of the amine is removed;

J is -A-B or -B;

A is C_{1-6} alkyl substituted with 0-3 R^e;

B is selected from C_3-C_{12} carbocycle and heterocycle wherein carbocycle and heterocycle are substituted with 0-5 R^{Ja};

R^{Ja} is selected from =O, F, Cl, Br, I, C_{1-6} haloalkyl, CN, NO_2, OH, NR^aR^a, OR^c, $C(=O)R^b$, CO_2R^c, $OC(=O)R^b$, $NR^aC(=O)R^b$, $C(=O)NR^aR^a$, $OC(=O)NR^aR^a$, $NR^aC(=O)OR^b$, $NR^aS(=O)_2R^b$, $S(=O)_2NR^aR^a$, $NR^aC(=S)R^b$, $C(=S)NR^aR^a$, $NR^aC(=O)NR^aR^a$, $NR^aC(=S)NR^aR^a$, $CH{=}NOR^c$, $CH{=}NR^a$, $CH{=}NNR^aR^a$, $C(=NR^a)NR^aR^a$, $NR^aC(=NR^a)NR^aR^a$,

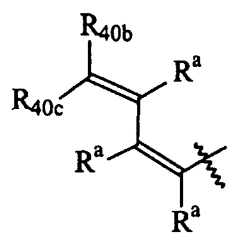
$(CH_2)_rS(O)_pR^b$, $O(CH_2)_qNR^aR^a$, $O(CH_2)_qOR^c$, $(CH_2)_rOR^d$, $(CH_2)_rC(=O)R^9$, $(CH_2)_rNHR^d$, $(CH_2)_rS(O)_pR^9$, C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, phenoxy, benzoyl, C_3-C_{12} carbocycle, and heterocycle, wherein phenoxy, benzoyl, carbocycle and heterocycle are substituted with 0-5 R^e;

r is selected from 0, 1, 2, 3, and 4;

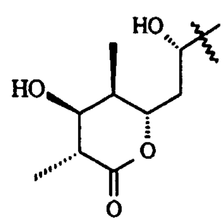
q is selected from 1, 2, 3, and 4; and

p is selected from 1 and 2;

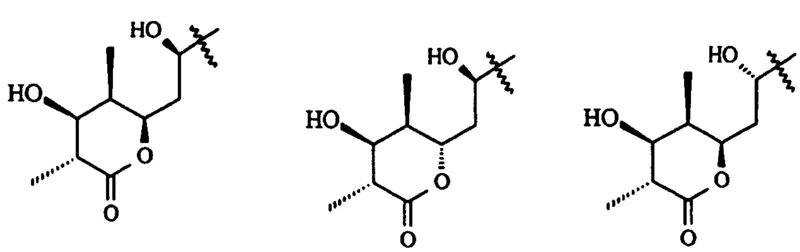
with the proviso that when R_1, R_2, R_6, R_7, and R_8 are methyl, R_3 is methyl or hydrogen, R_{25a} is oxygen, and R_4, R_9, R_{16}, R_{25b}, R_{25c} are hydrogen, R^{40a} is



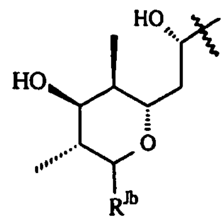
wherein R_{40b} and R_{40c} are hydrogen or one of R_{40b} and R_{40c} is hydrogen and the other is $(CH_2)_3OCOC(CH_3)_3$, J is other than



substituted with 0-2 $C(=O)CH_3$;



and



wherein R^{Jb} is S-phenyl or $O(CH_2)_2NHCOalkyl$.

2. The compound of claim 1 wherein:

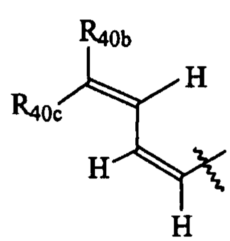
R_1, R_2, R_3, R_6, R_7, R_8, and R_{16} are independently selected from hydrogen and methyl;

R_{40} is $-OC(=O)NR_{25b}R_{25c}$;

R_{25b} and R_{25c} are independently selected from hydrogen, $S(O)_2R^b$, C_{1-6} alkyl, $(CH_2)_rC_3$-C_{12} carbocycle, and $(CH_2)_r$heterocycle, wherein alkyl, carbocycle, and heterocycle are substituted with 0-3 R_{25d};

alternatively, R_{25b} and R_{25c} may join with the nitrogen to which they are attached to form a five or six membered heterocycle containing 0-1 additional heteroatom selected from O, S, and N, wherein the heterocycle is optionally substituted with 0-3 R_{25d};

R_{40a} is



A is C_{1-3} alkyl substituted with 0-3 R^e;

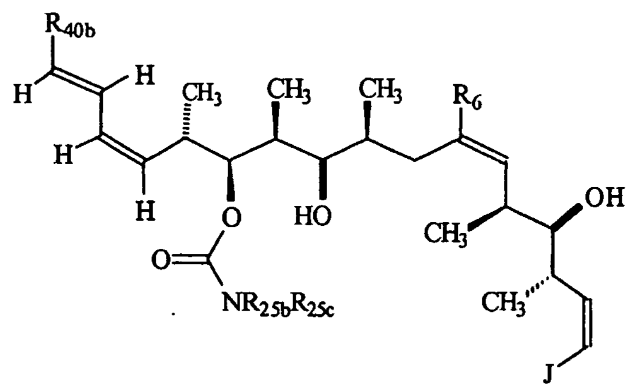
B is selected from C_3-C_6 carbocycle and a 5- or 6-membered heterocycle wherein carbocycle and heterocycle are

substituted with 0-5 R^{Ja};

r is selected from 0, 1, 2, and 3; and

q is selected from 1, 2, and 3.

3. The compound of claim 2 having the formula:



wherein R^6 is selected from hydrogen and methyl.

4. The compound of claim 3 wherein:

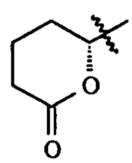
A is selected from CH_2 and CH_2CH_2, wherein the CH_2 and CH_2CH_2 are substituted with 0-1 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, and =O; and

B is selected from phenyl and a 5- or 6-membered heterocyle, wherein phenyl and heterocycle are substituted with 0-5 R^{Ja}.

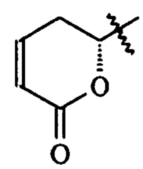
5. The compound of claim 4 wherein B is selected from phenyl, a 6-membered lactone ring, and a heterocycle selected from 2-pyrrolidonyl, 2H-pyrrolyl, 4-piperidonyl, 6H-1,2,5-thiadiazinyl, 2*H*,6*H*-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, morpholinyl, oxadiazolyl, 1,2,3-oxadiazolyl,

1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, tetrahydrofuranyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazole, wherein the phenyl, lactone ring, and heterocycle are substituted with 0-5 R^{Ja}.

6. The compound of claim 5 wherein B is selected from phenyl, pyridinyl, and a 6-membered lactone ring selected from the formulas:



and



wherein the phenyl, pyridinyl, and lactone ring is substituted with 0-3 R^{Ja}.

7. The compound of claim 6 wherein A is CH_2CH_2 substituted with 0-1 OH and R^{Ja} is selected from OH and methyl.

8. The compound of claim 7 wherein R_{40b} is hydrogen.

9. The compound of claim 7 wherein R_{25b} and R_{25c} are hydrogen.

10. The compound of claim 3 wherein R_{25b} and R_{25c} are independently selected from hydrogen, $S(O)_2R^b$, C_{1-6} alkyl, fluorenyl, and $(CH_2)_r$phenyl, wherein the alkyl and phenyl are substituted with 0-2 R_{25d};

R^b is selected from C_{1-6} alkyl, phenyl, benzyl, and phenethyl wherein R^b is substituted with 0-3 R^e;

R_{25d}, at each occurrence, is selected from hydrogen, F, Cl, Br, I, OH, OC_{1-6} alkyl, NO_2, CN, CF_3, CH_3, CO_2H, CO_2C_{1-6} alkyl, $OC(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $OC(=O)NH_2$, NH_2, NHC_{1-6} alkyl, $N(C_{1-6}\text{ alkyl})_2$ phenyl, phenoxy, benzoyl, and pyridinyl wherein phenyl, phenoxy, benzoyl, and pyridinyl are substituted with 0-3 R^e; and

R^e is selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, and NH_2.

11. The compound of claim 10 wherein R_{25b} is hydrogen and R_{25c} is selected from $S(O)_2C_{1-6}$ alkyl, C_{1-6} alkyl, fluorenyl, $S(O)_2$phenyl substituted with 0-3 R_{25d} selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, and NH_2; and phenyl substituted with 0-3 R_{25d} selected from phenyl, phenoxy, and benzoyl, wherein phenyl, phenoxy, and benzoyl are substituted with 0-3 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, and NH_2.

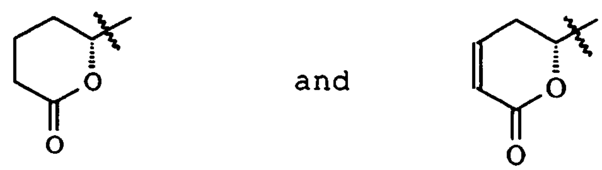
12. The compound of claim 11 wherein R_{40a} is hydrogen.

13. The compound of claim 11 wherein J is A-B, wherein:

A is CH_2CH_2 substituted with 0-1 OH; and

B is selected from phenyl, pyridinyl, and a 6-

membered lactone ring selected from the formulas:



wherein the phenyl, pyridinyl, and lactone ring is substituted with 0-3 R^{Ja} selected from OH and methyl.

14. The compound of claim 3 wherein R_{40b} is selected from hydrogen, C_{1-6} alkyl, $(CH_2)_rOC(=O)$phenyl, and $(CH_2)_r$phenyl, wherein the alkyl, $(CH_2)_rOC(=O)$phenyl, and phenyl are substituted with 0-3 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, phenyl, phenoxy, and benzoyl; and r is selected from 1 and 2.

15. The compound of claim wherein R_{40b} is selected from hydrogen, CH_2, CH_2CH_2, $CH_2CH_2CH_2$, and $(CH_2)_r$phenyl, wherein the CH_2, CH_2CH_2, $CH_2CH_2CH_2$, and phenyl are substituted with 0-1 R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, phenyl, phenoxy, and benzoyl.

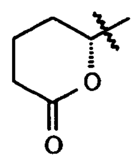
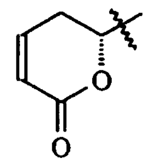
16. The compound of claim 15 wherein R_{25b} and R_{25c} are hydrogen.

17. The compound of claim 15 wherein:

J is A-B;

A is CH_2CH_2 substituted with 0-1 OH; and

B is selected from phenyl, pyridinyl, and a 6-membered lactone ring selected from the formulas:

 and 

wherein the phenyl, pyridinyl, and lactone ring is substituted with 0-3 R^{Ja} selected from OH and methyl.

18. The compound of claim 3 wherein:

R_{40b} is selected from hydrogen, C_{1-6} alkyl, $(CH_2)_rOC(=O)$phenyl, and $(CH_2)_r$phenyl, wherein the alkyl, $(CH_2)_rOC(=O)$phenyl, and phenyl are substituted with 0-3 R^e;

R_{25b} and R_{25c} are independently selected from hydrogen, $S(O)_2R^b$, C_{1-6} alkyl, fluorenyl, and $(CH_2)_r$phenyl, wherein the alkyl and phenyl are substituted with 0-2 R_{25d};

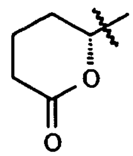
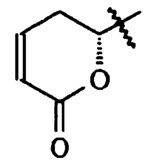
R^b is selected from C_{1-6} alkyl, phenyl, benzyl, and phenethyl wherein R^b is substituted with 0-3 R^e;

R_{25d}, at each occurrence, is selected from hydrogen, F, Cl, Br, I, OH, OC_{1-6} alkyl, NO_2, CN, CF_3, CH_3, CO_2H, CO_2C_{1-6} alkyl, $OC(=O)C_{1-6}$ alkyl, $C(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $NHC(=O)C_{1-6}$ alkyl, $OC(=O)NH_2$, NH_2, NHC_{1-6} alkyl, $N(C_{1-6}$ alkyl$)_2$ phenyl, phenoxy, benzoyl, and pyridinyl wherein phenyl, phenoxy, benzoyl, and pyridinyl are substituted with 0-3 R^e; and

R^e selected from F, Cl, Br, I, OH, OCH_3, NO_2, CN, CF_3, CH_3, CO_2H, CO_2CH_3, $OC(=O)CH_3$, $C(=O)CH_3$, $NHC(=O)CH_3$, $NHC(=O)CH_3$, $OC(=O)NH_2$, NH_2, phenyl, phenoxy, and benzoyl;

A is CH_2CH_2 substituted with 0-1 OH;

B is selected from phenyl, pyridinyl, and a 6-membered lactone ring selected from the formulas:

 and 

wherein the phenyl, pyridinyl, and lactone ring is substituted with 0-3 R^{Ja} selected from OH and methyl; and

r is selected from 1 and 2.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

20. A method for stabilizing microtubules, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1.

Figure 1

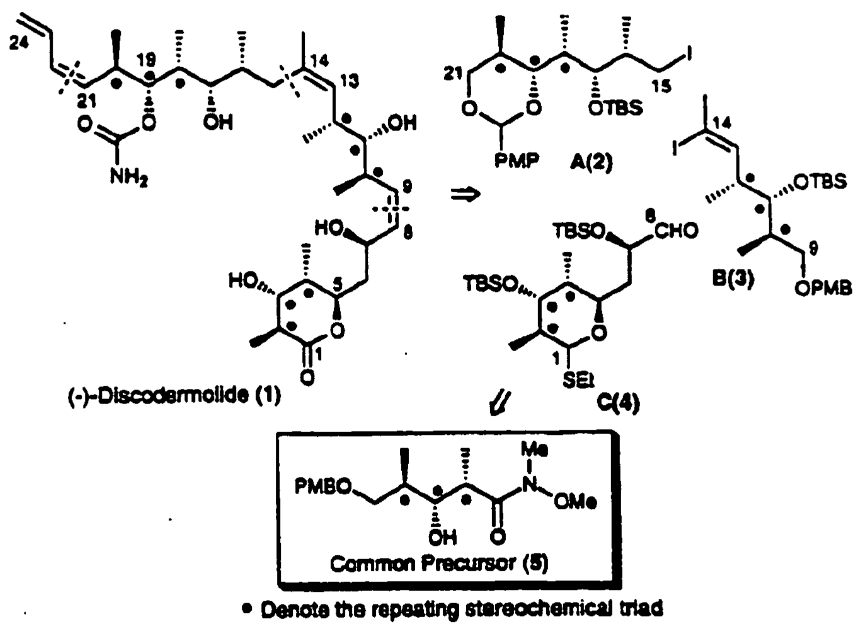


Figure 2

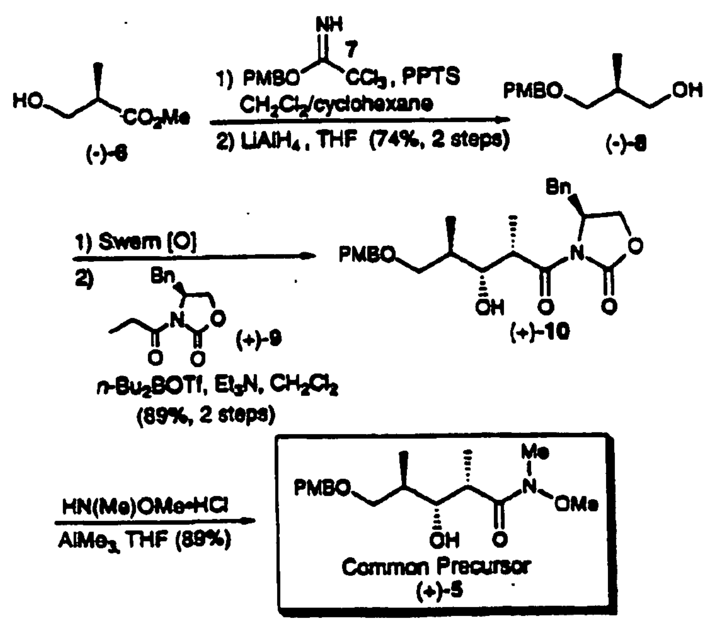


Figure 3

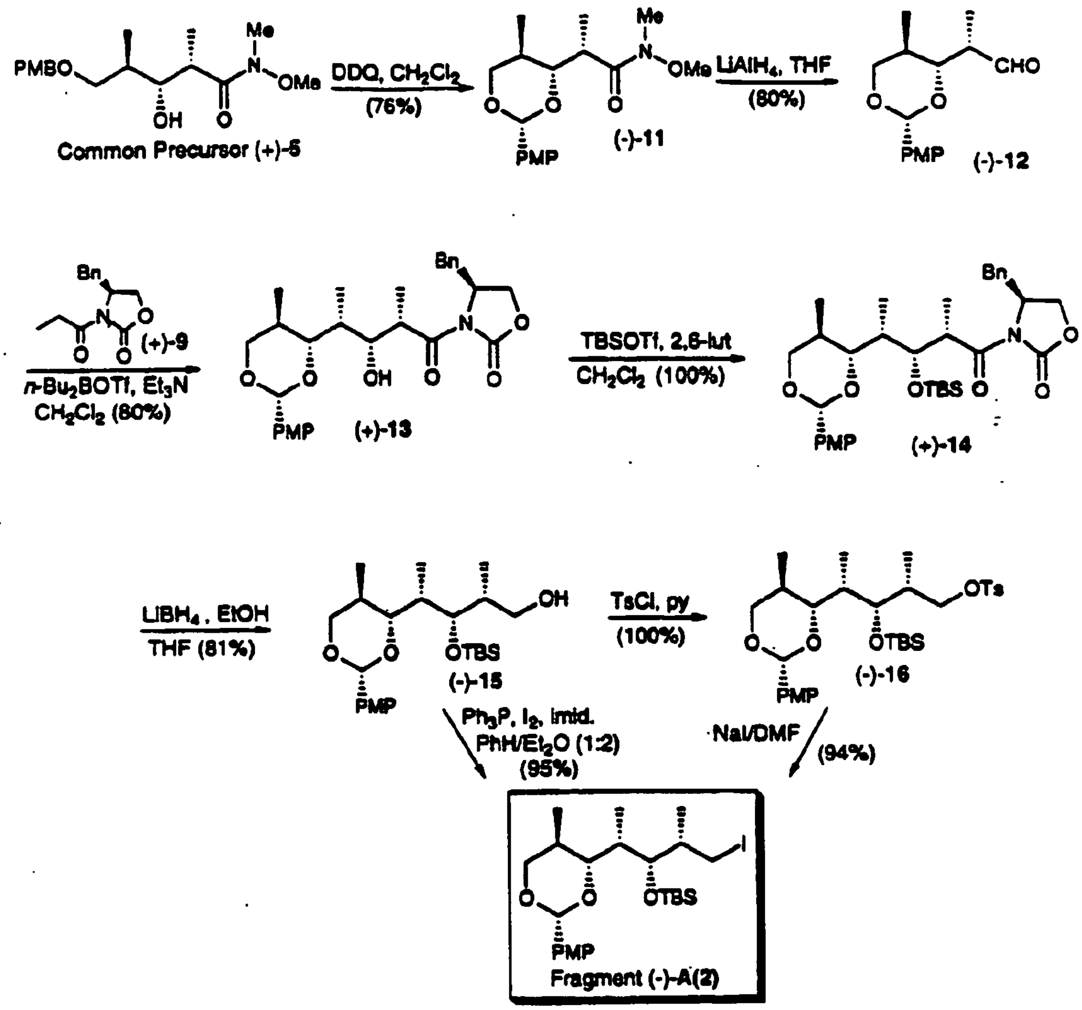

PMBO
Me
N
OMe
OH
O
Common Precursor (+)-5
DDQ, CH2Cl2
(76%)
PMP
(-)-11
LiAlH4, THF
(80%)
CHO
(-)-12
Bn
(+)-9
n-Bu2BOTf, Et3N
CH2Cl2 (80%)
(+)-13
TBSOTf, 2,6-lut
CH2Cl2 (100%)
OTBS
(+)-14
LiBH4, EtOH
THF (81%)
OH
(-)-15
TsCl, py
(100%)
OTs
(-)-16
Ph3P, I2, imid.
PhH/Et2O (1:2)
(95%)
NaI/DMF
(94%)
I
Fragment (-)-A(2)

Figure 4

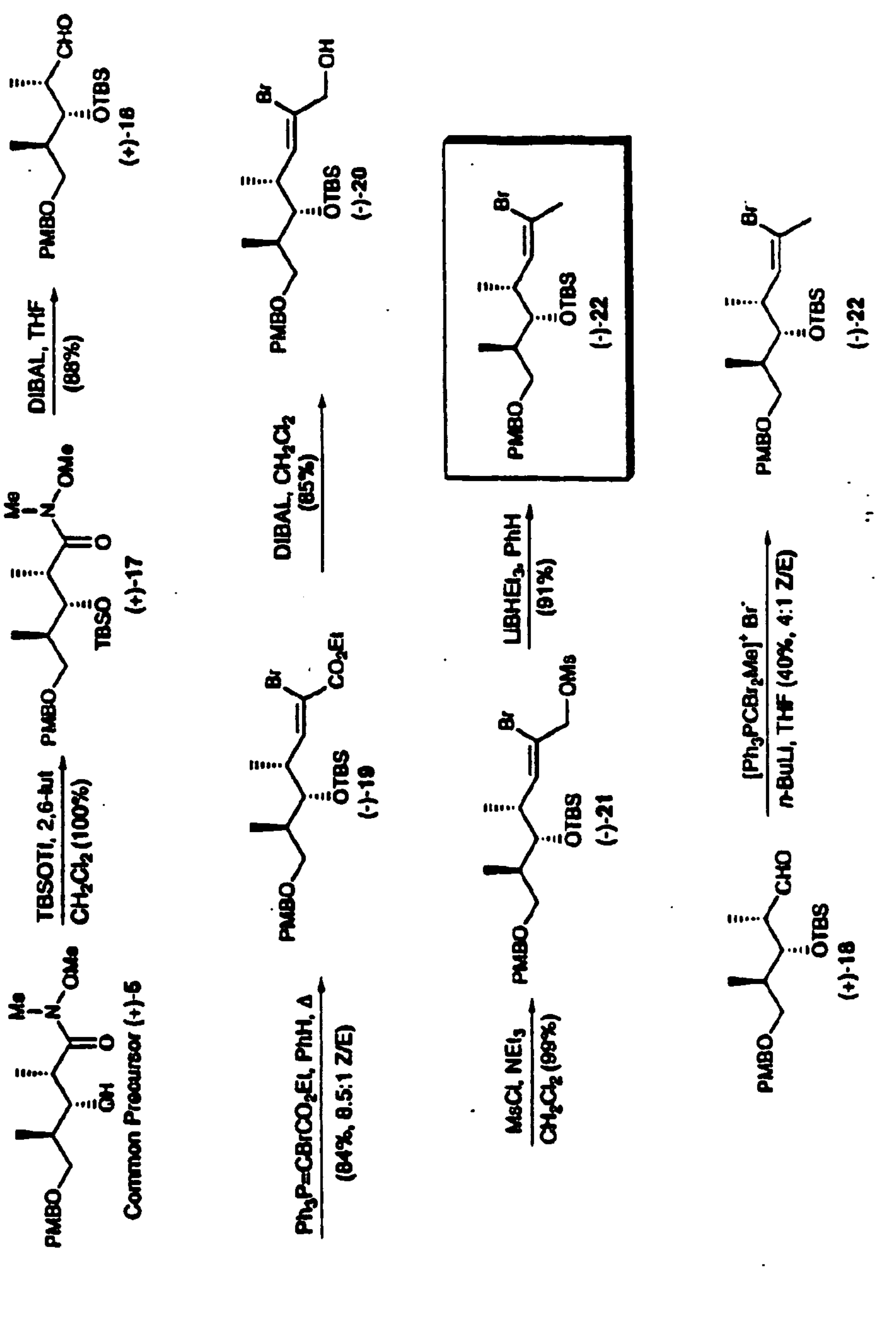

PMBO
Me
N
OMe
OH
O
Common Precursor (+)-5
TBSOTf, 2,6-lut
CH2Cl2 (100%)
TBSO
(+)-17
DIBAL, THF
(88%)
CHO
OTBS
(+)-16
Ph3P=CBrCO2Et, PhH, Δ
(84%, 8.5:1 Z/E)
Br
CO2Et
(-)-19
DIBAL, CH2Cl2
(85%)
OH
(-)-20
MsCl, NEt3
CH2Cl2 (99%)
OMs
(-)-21
LiBHEt3, PhH
(91%)
(-)-22
[Ph3PCBr2Me]+ Br-
n-BuLi, THF (40%, 4:1 Z/E)
(+)-16
(-)-22

Figure 5

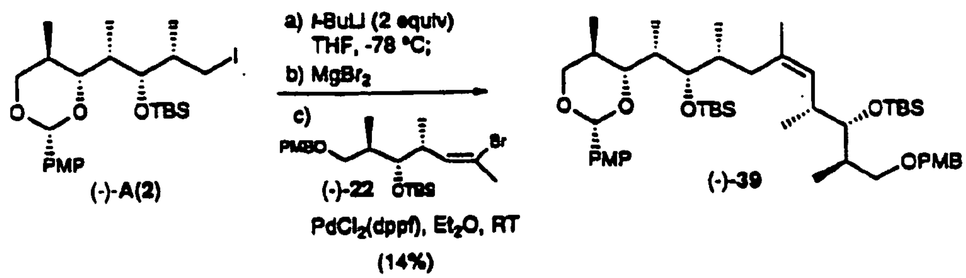


Figure 6

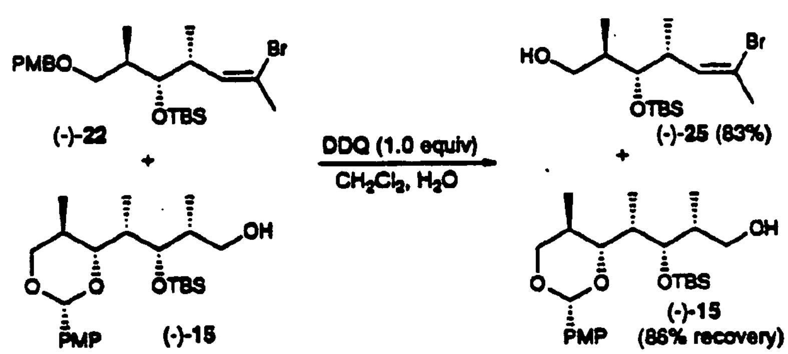


Figure 7

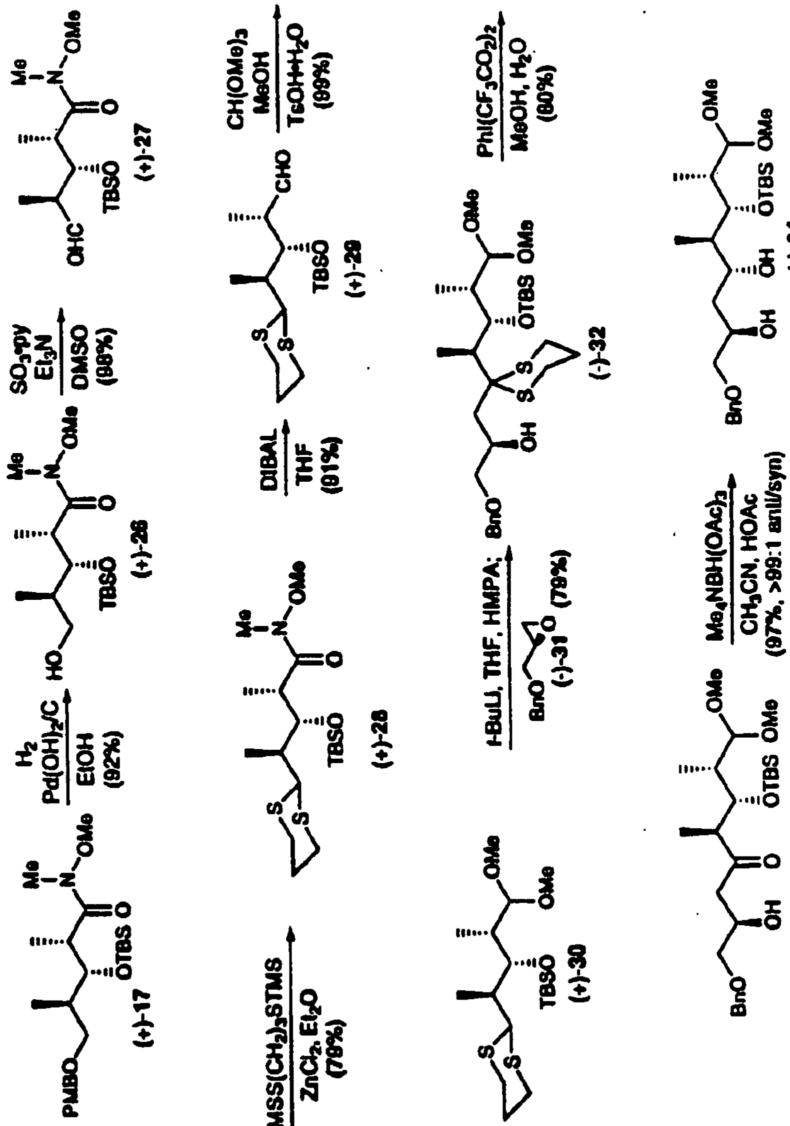

(+)-17
H_2
$Pd(OH)_2/C$
EtOH
(92%)
(+)-26
SO_3•py
Et_3N
DMSO
(98%)
(+)-27
$TMSS(CH_2)_3STMS$
$ZnCl_2$, Et_2O
(78%)
(+)-28
DIBAL
THF
(91%)
(+)-29
$CH(OMe)_3$
MeOH
TsOH•H_2O
(99%)
(+)-30
t-BuLi, THF, HMPA;
(-)-31
(79%)
(-)-32
$PhI(CF_3CO_2)_2$
MeOH, H_2O
(80%)
(+)-33
$Me_4NBH(OAc)_3$
CH_3CN, HOAc
(97%, >99:1 anti/syn)
(-)-34

Figure 8

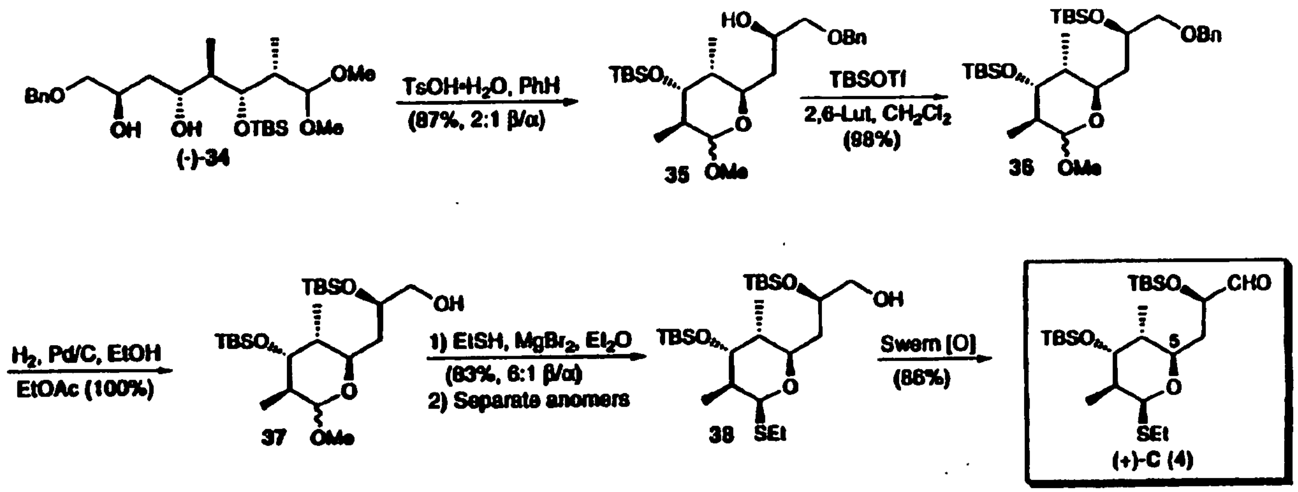


Figure 9

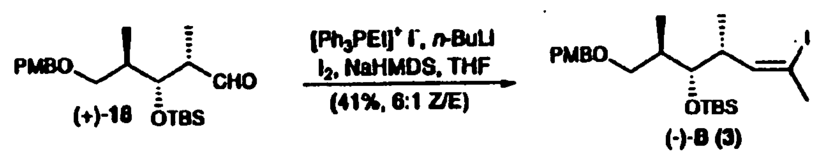


Figure 10

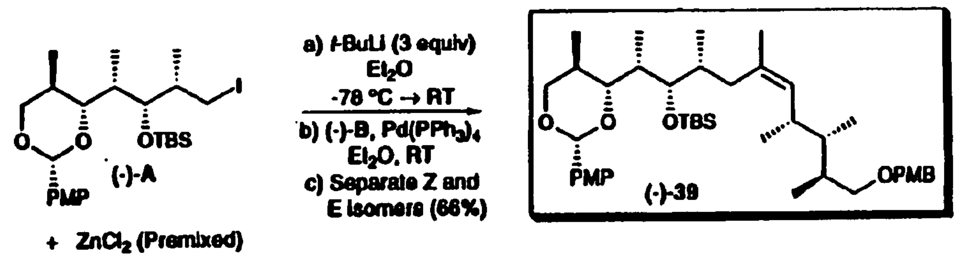
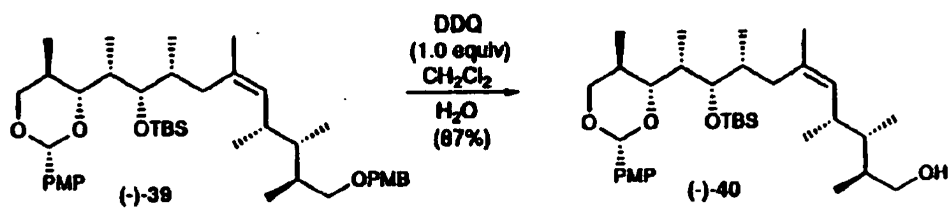


Figure 11



7/57

Figure 12

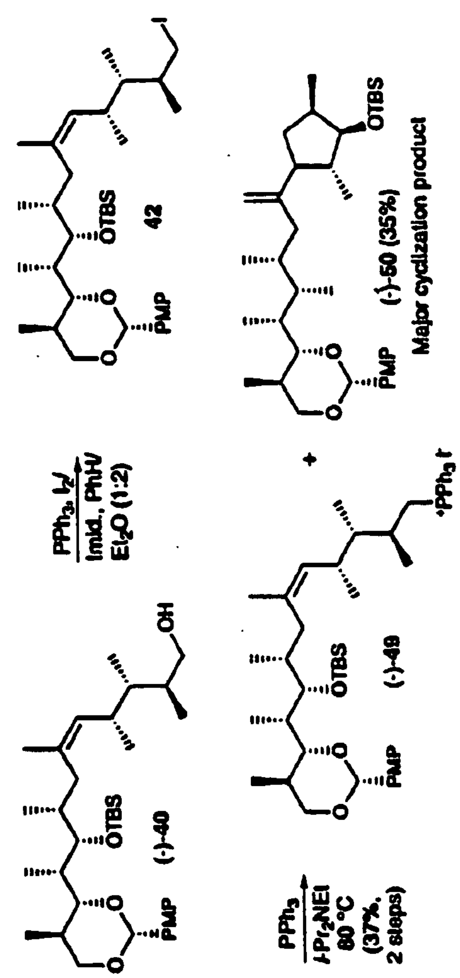

OTBS
PMP
(-)-40
OH
PPh3, I2
Imid., PhH/Et2O (1:2)
42
PPh3
i-Pr2NEt
80 °C
(37%, 2 steps)
(-)-49
+PPh3 I-
+
(-)-50 (35%)
Major cyclization product

Figure 13

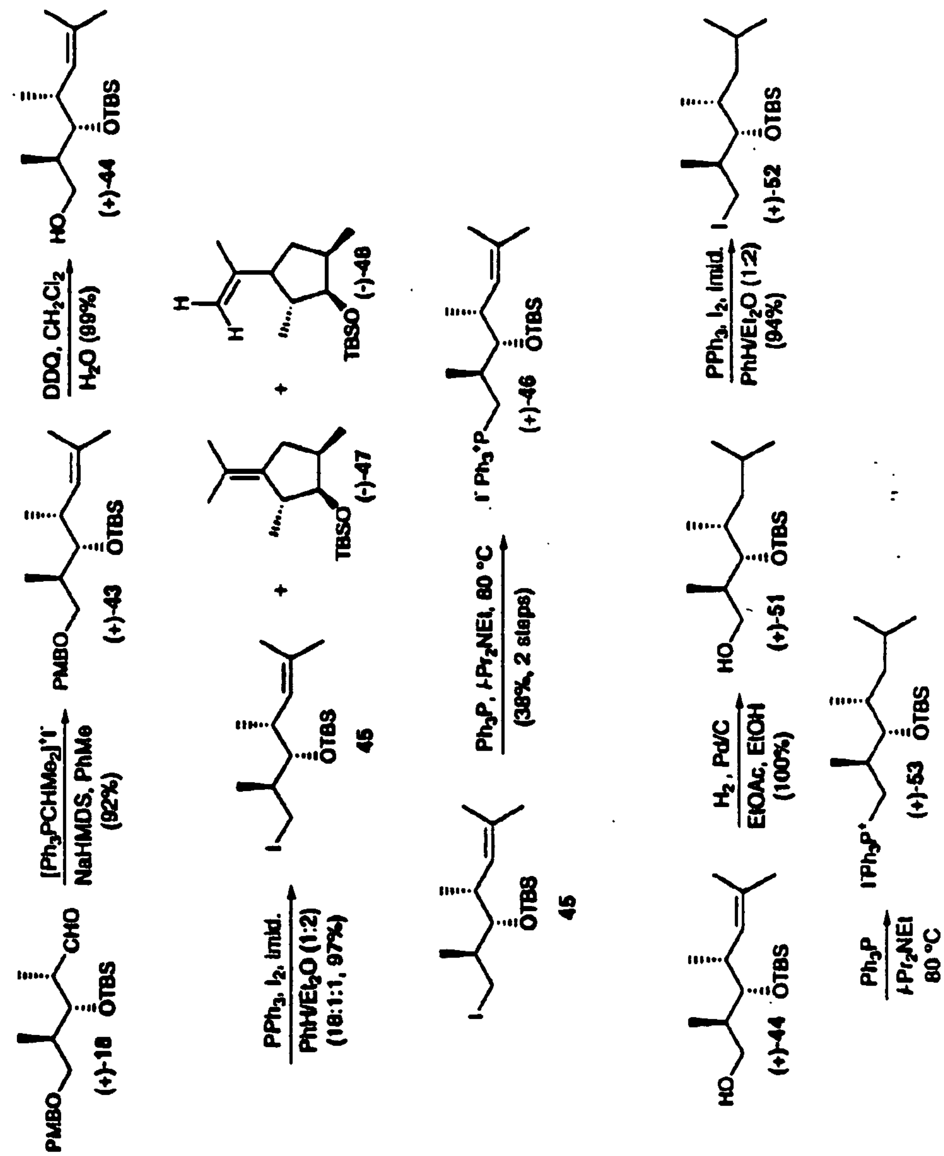
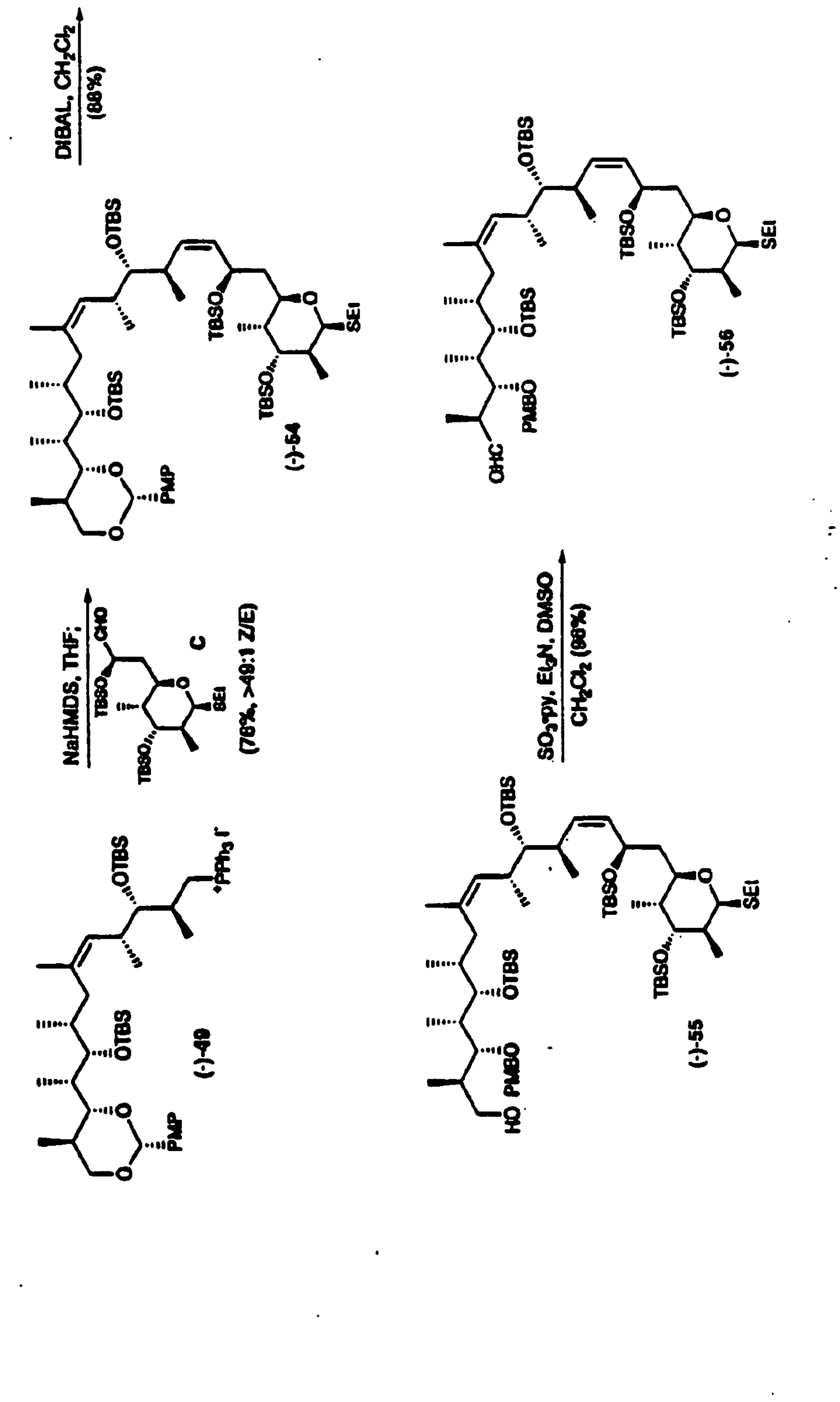

PMBO
OTBS
CHO
(+)-18
[Ph$_3$PCHMe$_2$]$^+$I$^-$
NaHMDS, PhMe
(92%)
PMBO
OTBS
(+)-43
DDQ, CH$_2$Cl$_2$
H$_2$O (99%)
HO
OTBS
(+)-44
PPh$_3$, I$_2$, imid.
PhH/Et$_2$O (1:2)
(18:1:1, 97%)
I
OTBS
45
+
TBSO
(-)-47
+
H
H
TBSO
(-)-48
I
OTBS
45
Ph$_3$P, i-Pr$_2$NEt, 80 °C
(38%, 2 steps)
I$^-$ Ph$_3$$^+$P
OTBS
(+)-46
HO
OTBS
(+)-44
H$_2$, Pd/C
EtOAc, EtOH
(100%)
HO
OTBS
(+)-51
PPh$_3$, I$_2$, imid.
PhH/Et$_2$O (1:2)
(94%)
I
OTBS
(+)-52
Ph$_3$P
i-Pr$_2$NEt
80 °C
(94%)
IPh$_3$P$^+$
OTBS
(+)-53

Figure 14


DIBAL, CH2Cl2
(88%)
NaHMDS, THF;
(76%, >49:1 Z/E)
SO3·py, Et3N, DMSO
CH2Cl2 (98%)
(-)-49
(-)-54
(-)-55
(-)-56
C
OTBS
TBSO
PMP
PMBO
SEt
OHC
HO

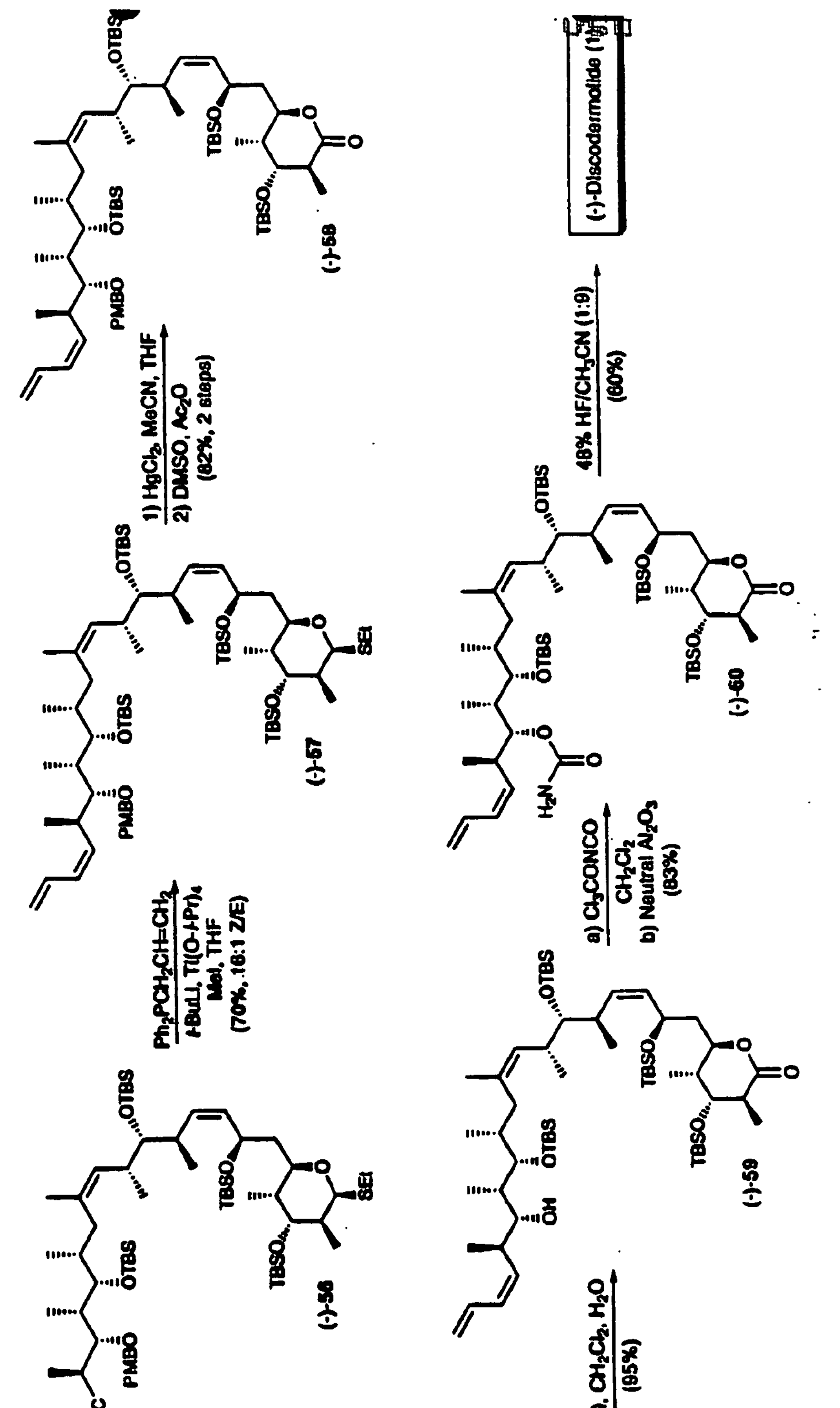

OHC
PMBO
OTBS
TBSO
SEt
(-)-56
$Ph_2PCH_2CH=CH_2$
t-BuLi, $Ti(O\text{-}i\text{-}Pr)_4$
MeI, THF
(70%, 16:1 Z/E)
(-)-57
1) $HgCl_2$, MeCN, THF
2) DMSO, Ac_2O
(82%, 2 steps)
(-)-58
DDQ, CH_2Cl_2, H_2O
(95%)
OH
(-)-59
a) Cl_3CONCO
CH_2Cl_2
b) Neutral Al_2O_3
(83%)
H_2N
(-)-60
48% HF/CH_3CN (1:9)
(60%)
(-)-Discodermolide (1)

Figure 15

Figure 16

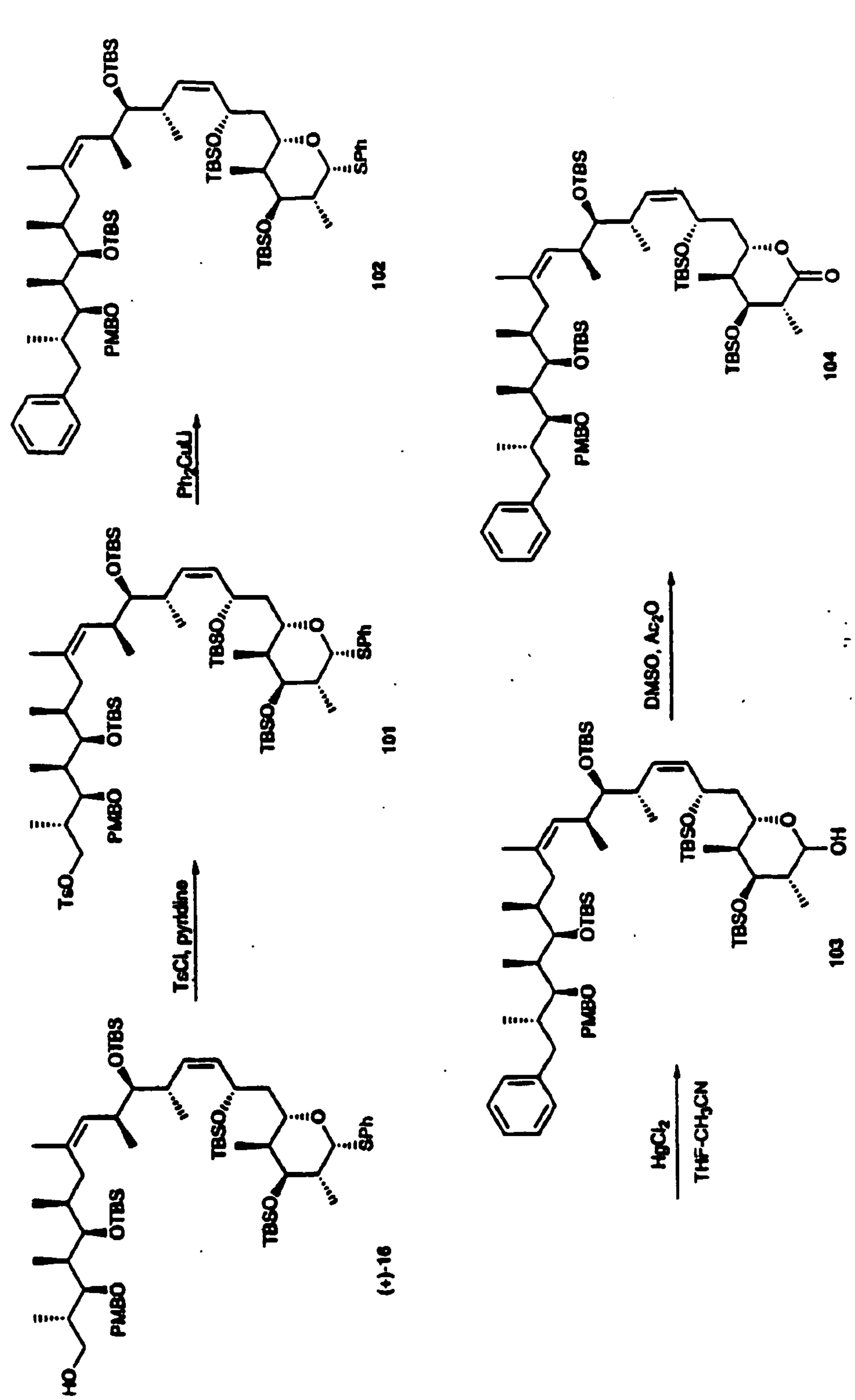

HO
PMBO
OTBS
OTBS
TBSO
TBSO
SPh
(+)-16
TsCl, pyridine
TsO
101
Ph$_2$CuLi
102
HgCl$_2$
THF-CH$_3$CN
OH
103
DMSO, Ac$_2$O
104

Figure 17

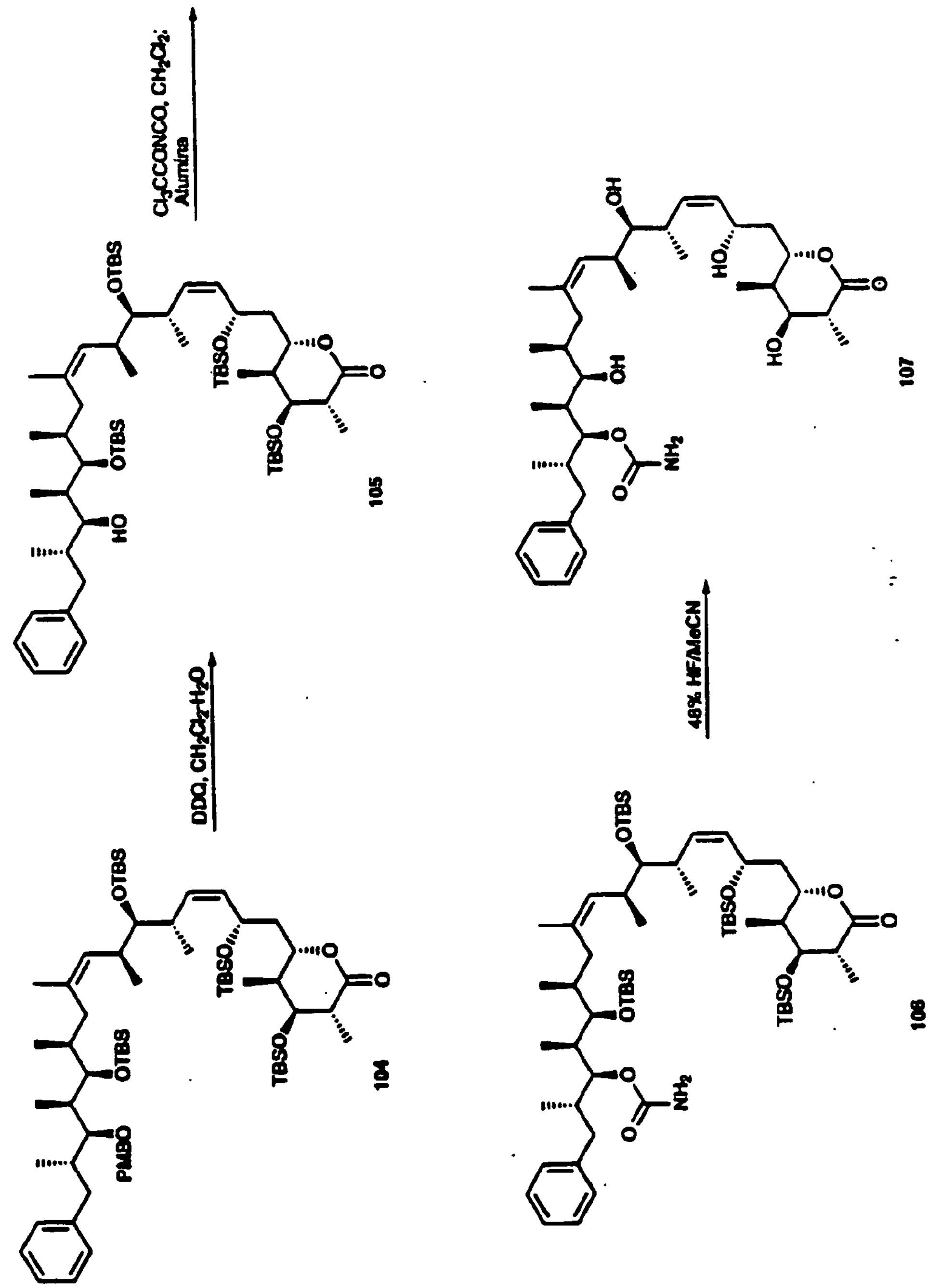

104
DDQ, CH2Cl2-H2O
105
Cl3CCONCO, CH2Cl2;
Alumina
106
48% HF/MeCN
107

Figure 18

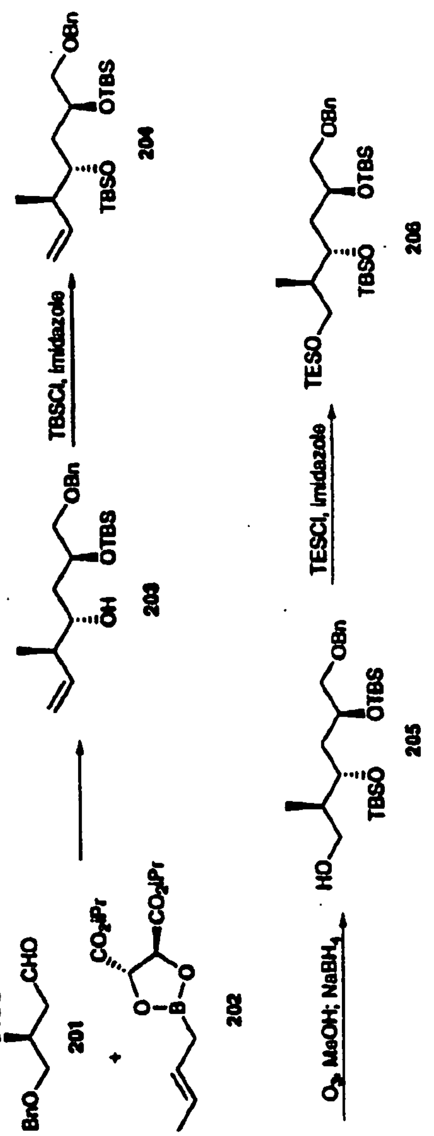

201
202
203
TBSCl, imidazole
204
O3, MeOH; NaBH4
205
TESCl, imidazole
206

Figure 19

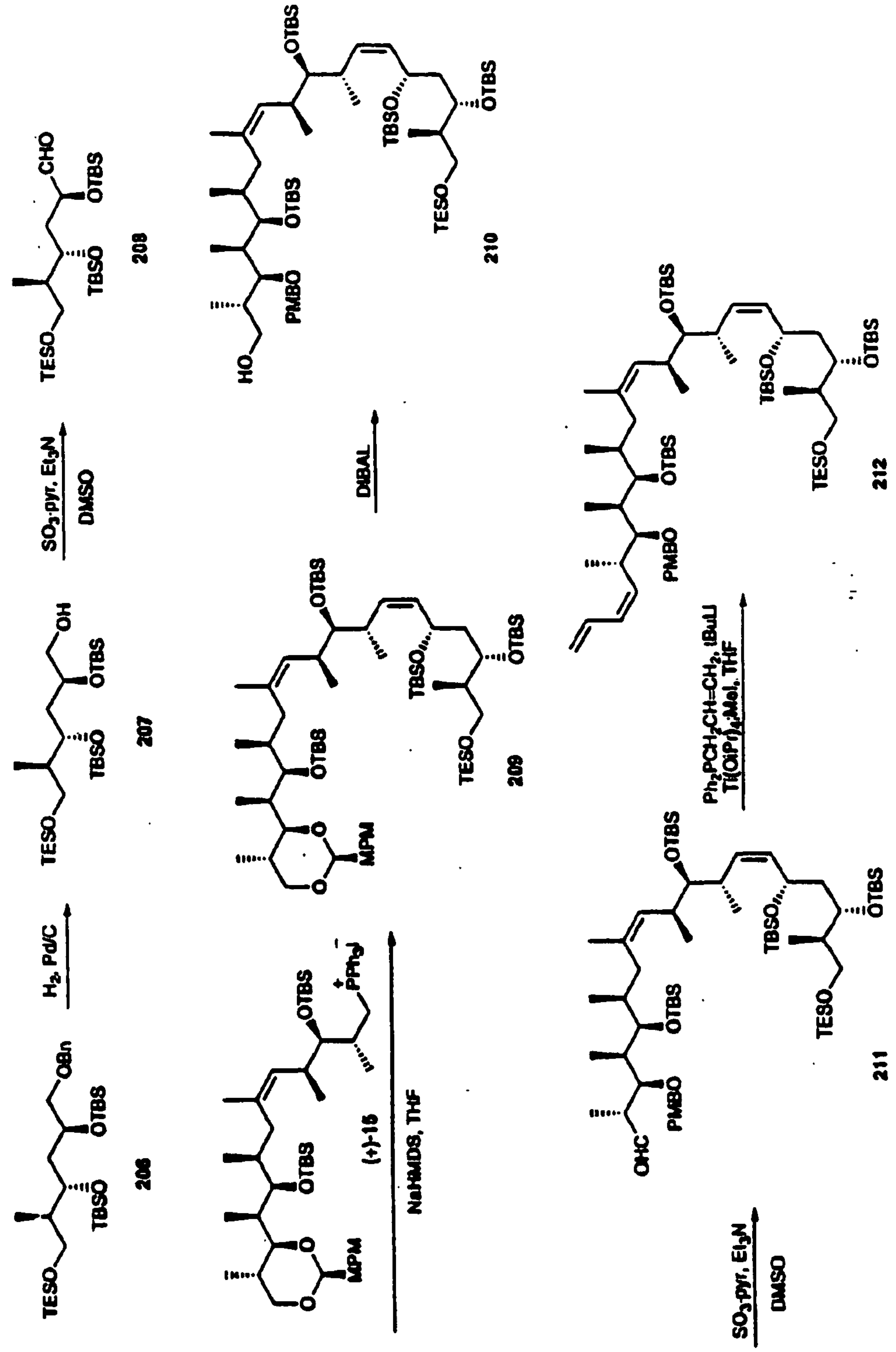

TESO
TBSO
OTBS
OBn
206
H_2, Pd/C
OH
207
SO_3·pyr, Et_3N
DMSO
CHO
208
MPM
(+)-15
NaHMDS, THF
209
DIBAL
HO
PMBO
210
SO_3·pyr, Et_3N
DMSO
OHC
211
$Ph_2PCH_2CH=CH_2$, tBuLi
$Ti(OiPr)_4$;MeI, THF
212

Figure 20

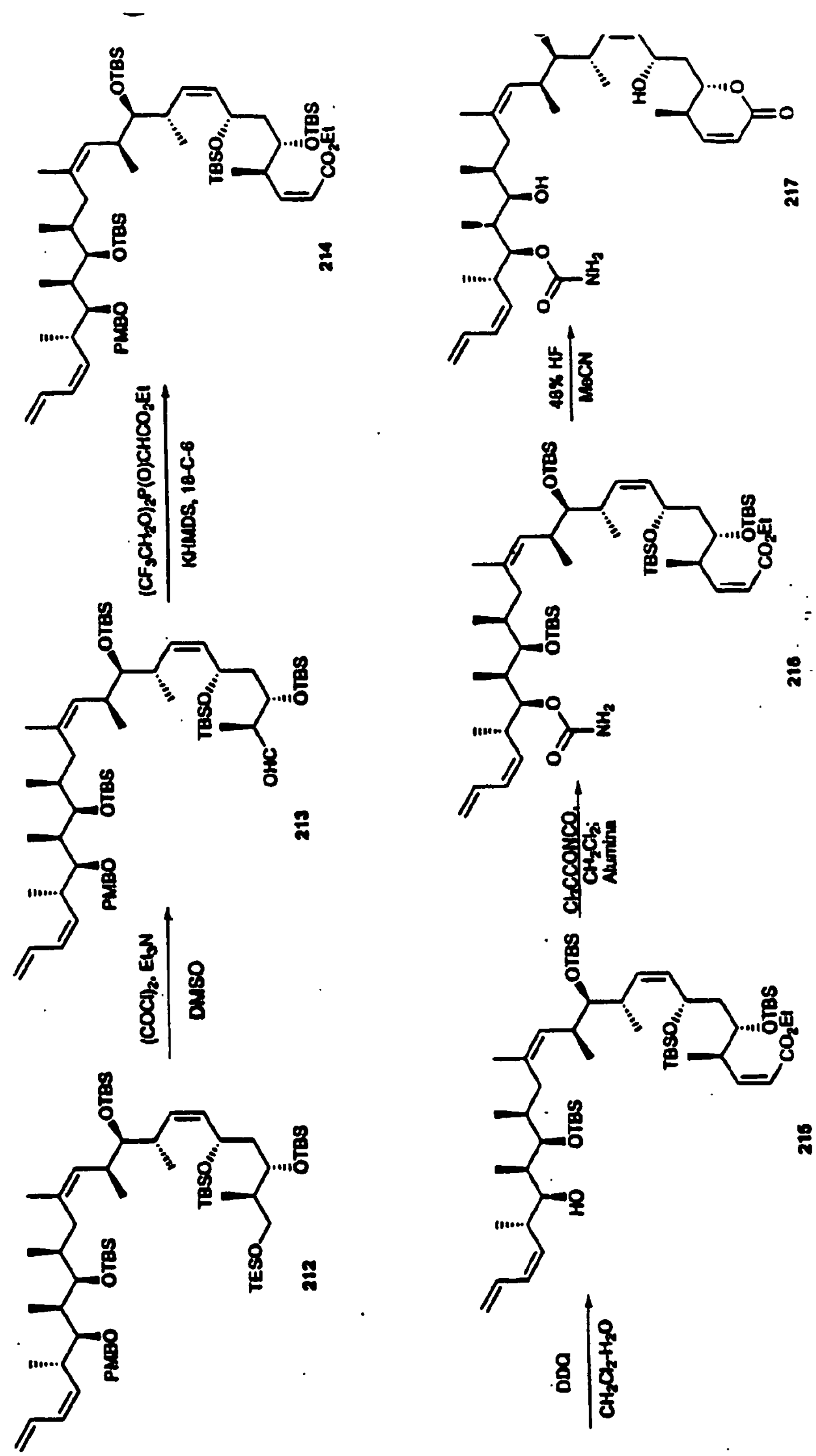

212
213
214
215
216
217
$(COCl)_2$, Et_3N
DMSO
$(CF_3CH_2O)_2P(O)CHCO_2Et$
KHMDS, 18-C-6
DDQ
CH_2Cl_2-H_2O
$Cl_3CCONCO$
CH_2Cl_2;
Alumina
48% HF
MeCN
PMBO
OTBS
TBSO
TESO
OHC
CO_2Et
HO
OH
NH_2

Figure 21

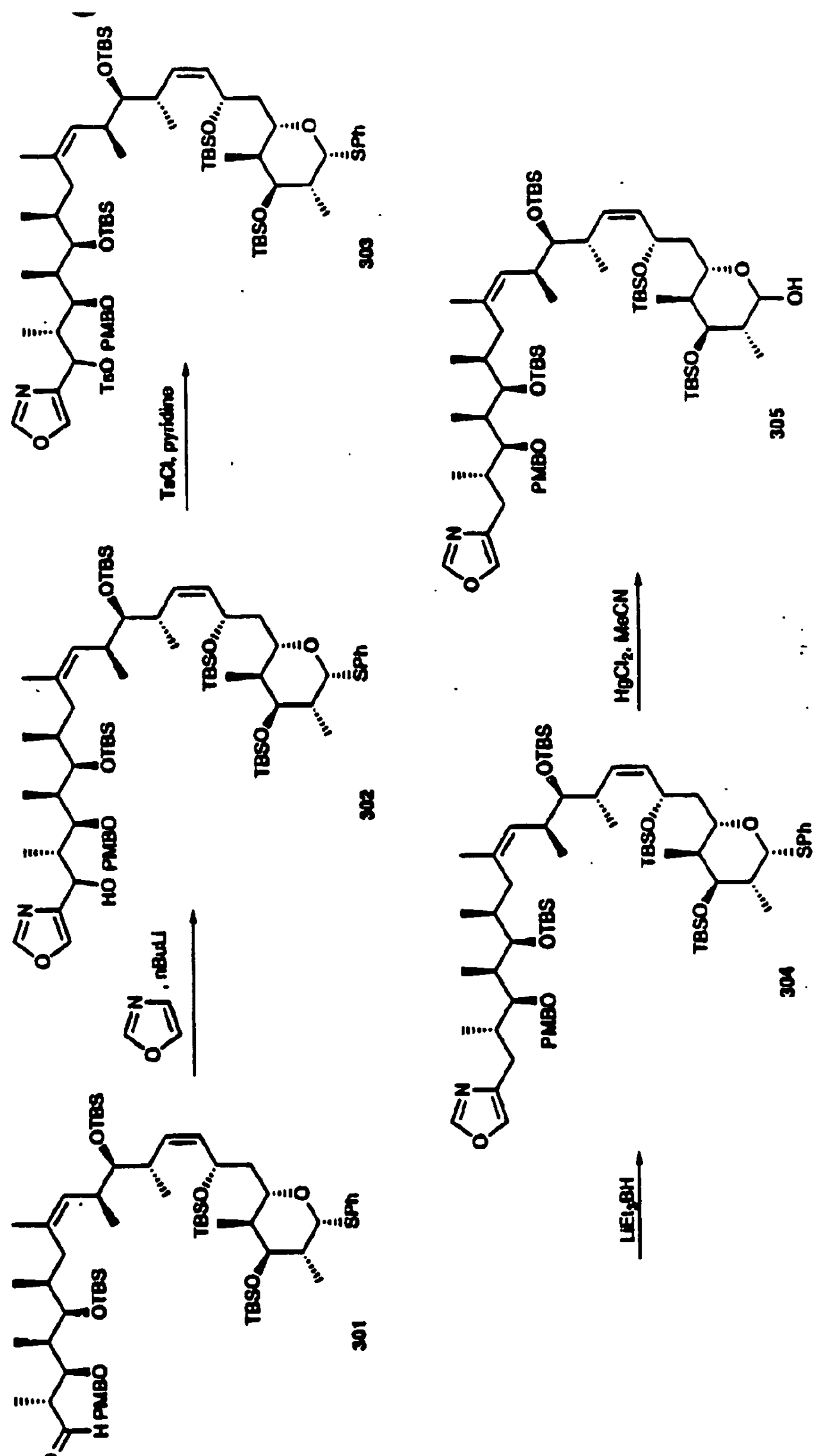


Figure 22

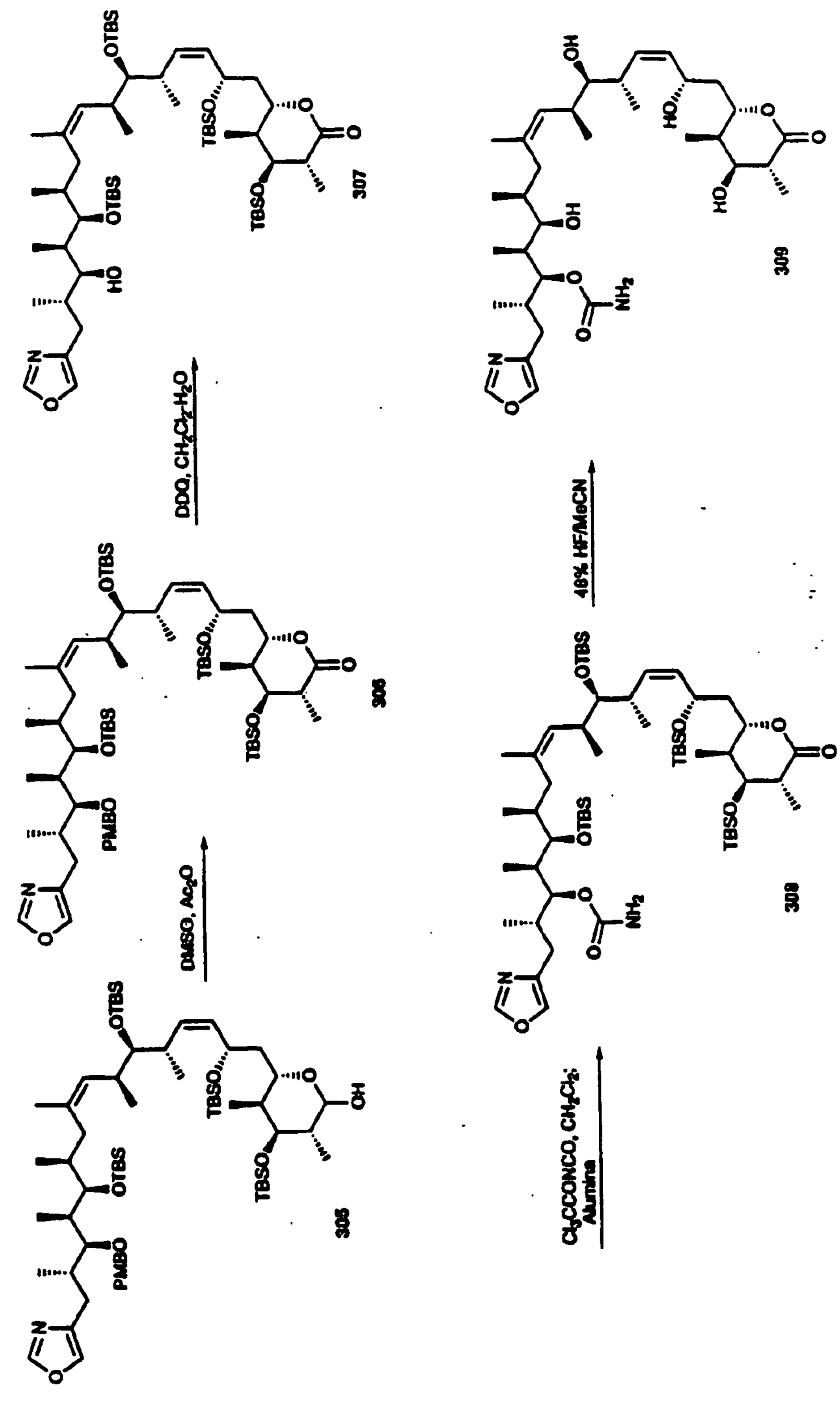

DMSO, Ac_2O
DDQ, CH_2Cl_2-H_2O
$Cl_3CCONCO$, CH_2Cl_2; Alumina
46% HF/MeCN
305
306
307
308
309

Figure 23

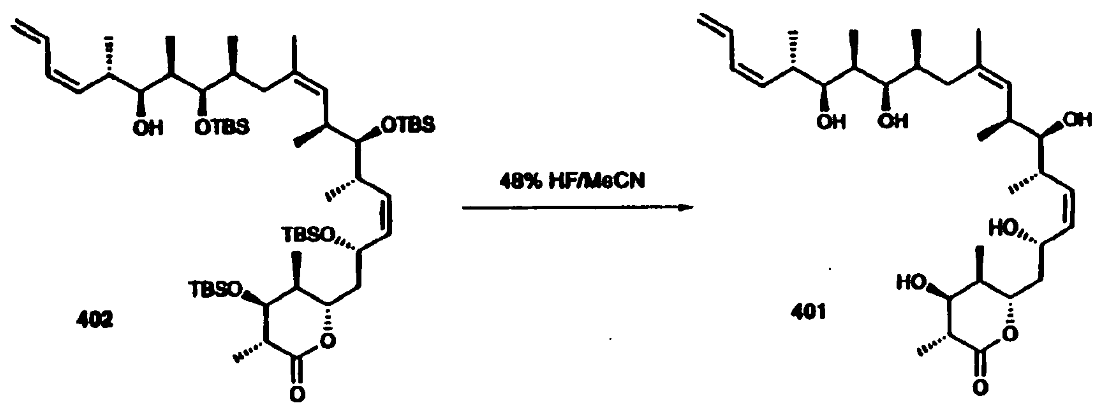


Figure 24

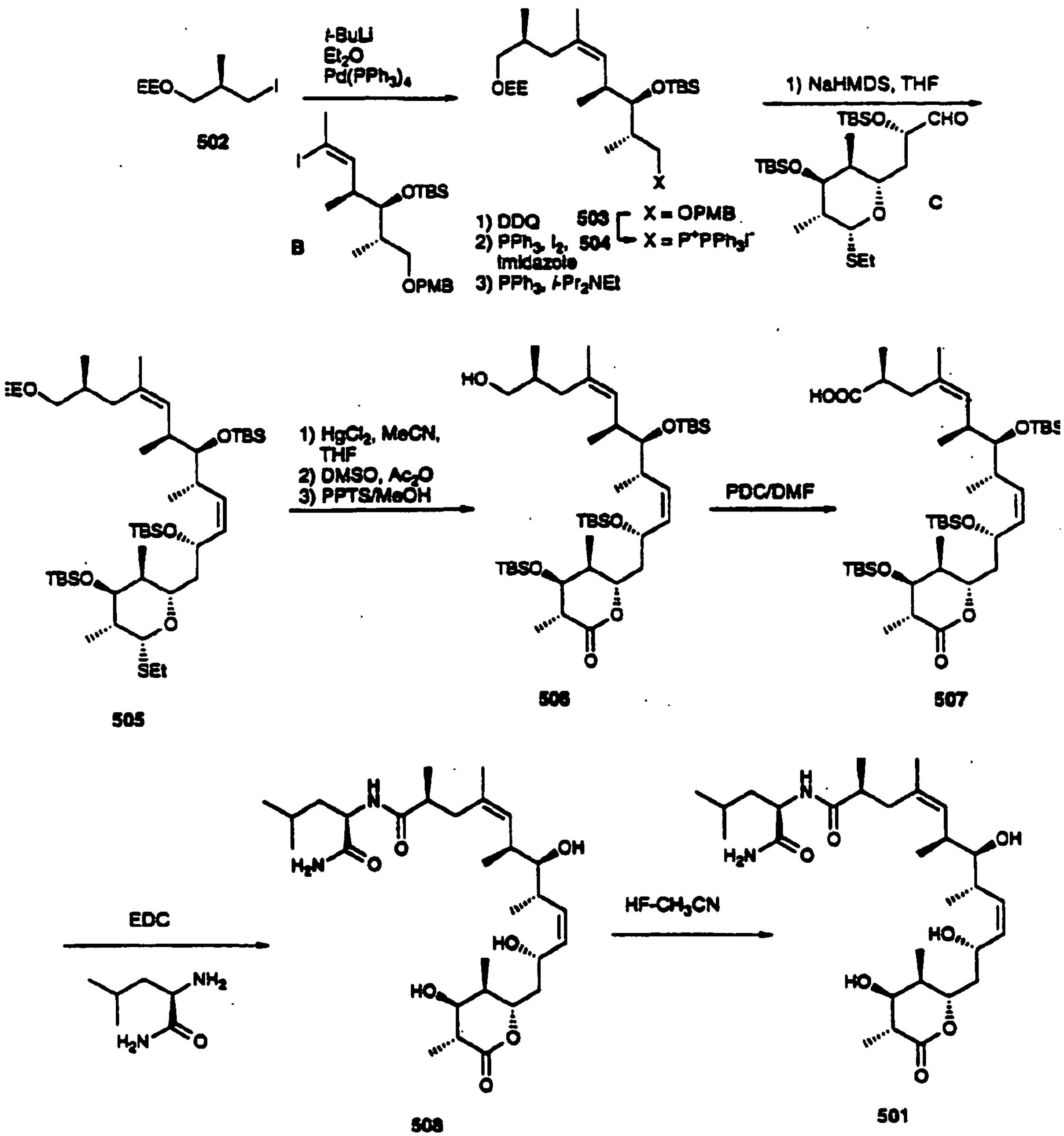
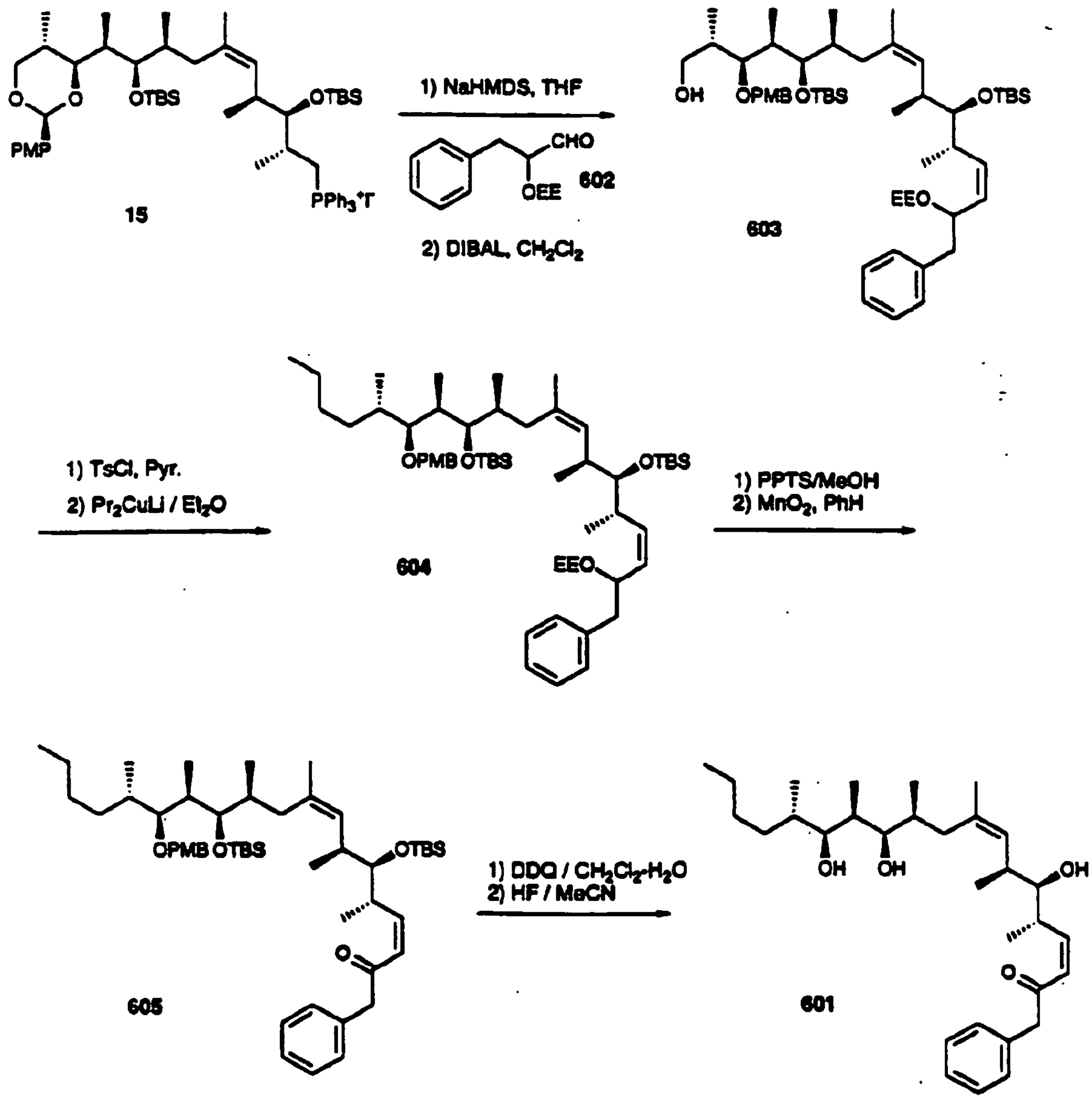
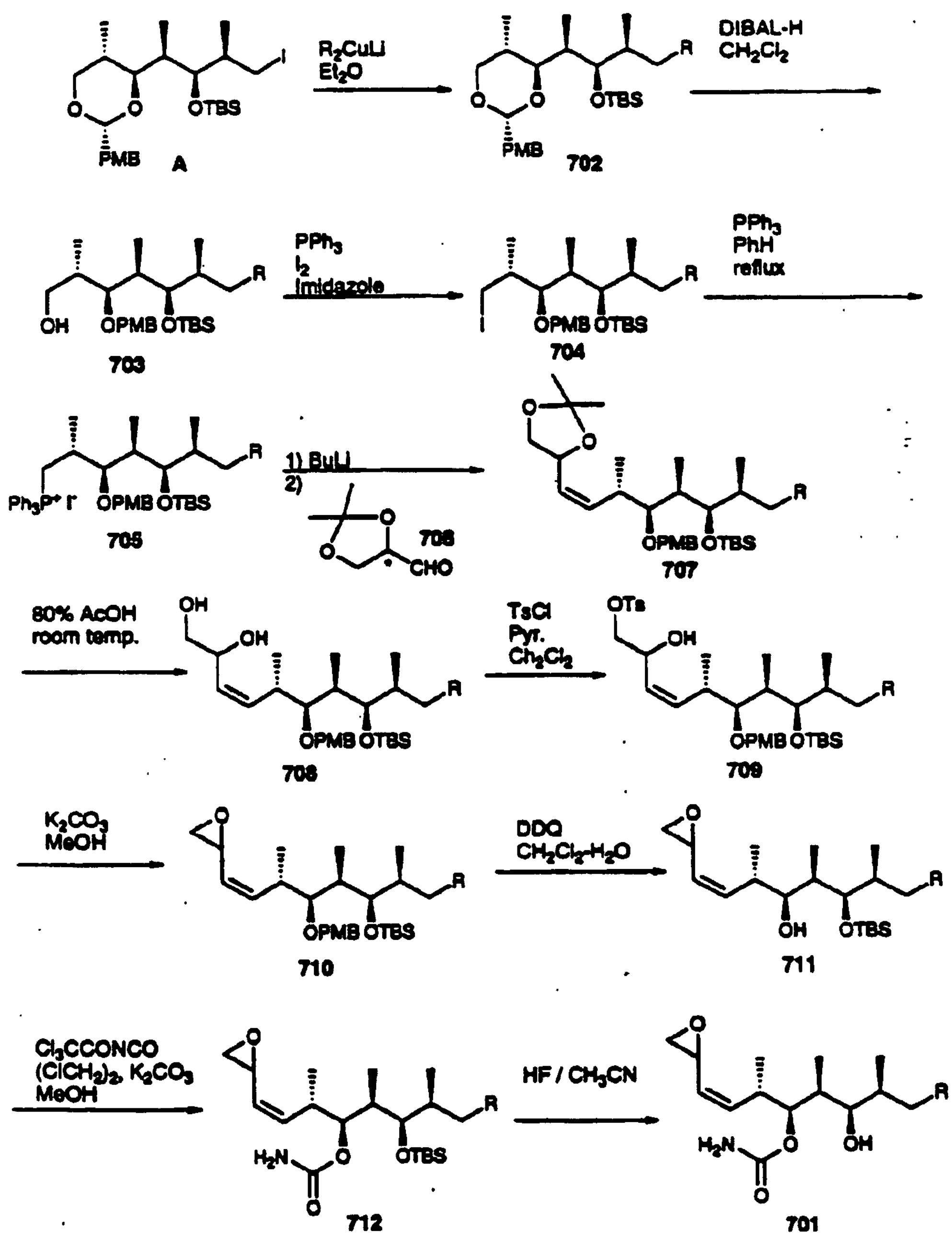

EEO
502
t-BuLi
Et$_2$O
Pd(PPh$_3$)$_4$
B
OTBS
OPMB
OEE
X
1) DDQ
2) PPh$_3$, I$_2$, imidazole
3) PPh$_3$, i-Pr$_2$NEt
503 X = OPMB
504 X = P$^+$PPh$_3$I$^-$
1) NaHMDS, THF
TBSO
CHO
SEt
C
505
1) HgCl$_2$, MeCN, THF
2) DMSO, Ac$_2$O
3) PPTS/MeOH
HO
506
PDC/DMF
HOOC
507
EDC
NH$_2$
H$_2$N
OH
508
HF-CH$_3$CN
501

Figure 25



PMP
OTBS
OTBS
PPh3+I-
15
1) NaHMDS, THF
CHO
OEE
602
2) DIBAL, CH2Cl2
OH
OPMB
OTBS
OTBS
EEO
603
1) TsCl, Pyr.
2) Pr2CuLi / Et2O
OPMB
OTBS
OTBS
EEO
604
1) PPTS/MeOH
2) MnO2, PhH
OPMB
OTBS
OTBS
O
605
1) DDQ / CH2Cl2-H2O
2) HF / MeCN
OH
OH
OH
O
601

Figure 26



R2CuLi
Et2O
OTBS
PMB
A
DIBAL-H
CH2Cl2
702
PPh3
I2
imidazole
OH
OPMB OTBS
703
704
PPh3
PhH
reflux
Ph3P+ I-
705
1) BuLi
2)
706
CHO
707
80% AcOH
room temp.
708
TsCl
Pyr.
CH2Cl2
OTs
709
K2CO3
MeOH
710
DDQ
CH2Cl2-H2O
711
Cl3CCONCO
(ClCH2)2, K2CO3
MeOH
H2N
712
HF / CH3CN
701
R

Figure 27

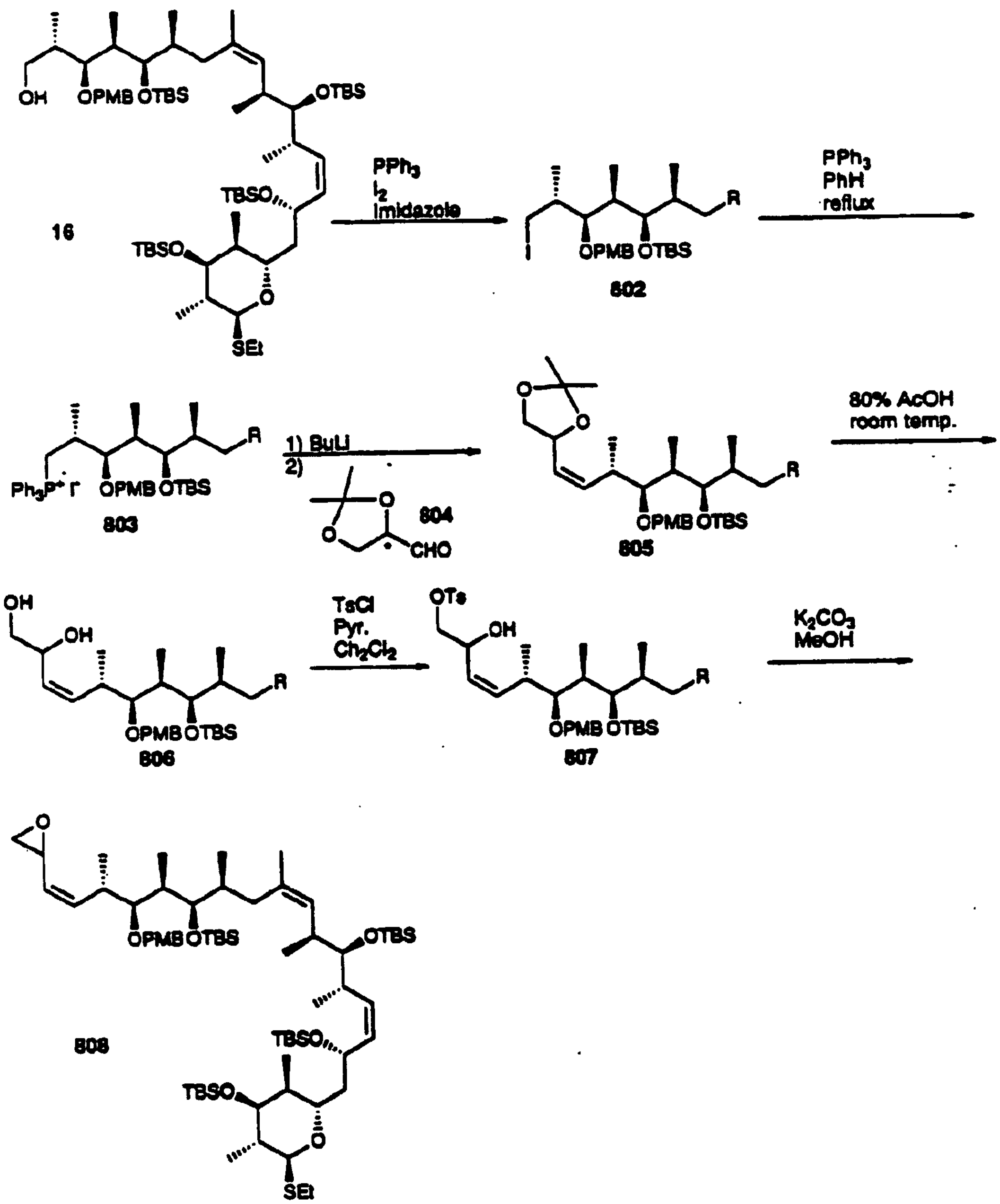

OH
OPMB
OTBS
TBSO
SEt
16
PPh3
I2
imidazole
R
802
PPh3
PhH
reflux
Ph3P+ I-
803
1) BuLi
2)
CHO
804
805
80% AcOH
room temp.
806
TsCl
Pyr.
CH2Cl2
OTs
807
K2CO3
MeOH
808

Figure 28

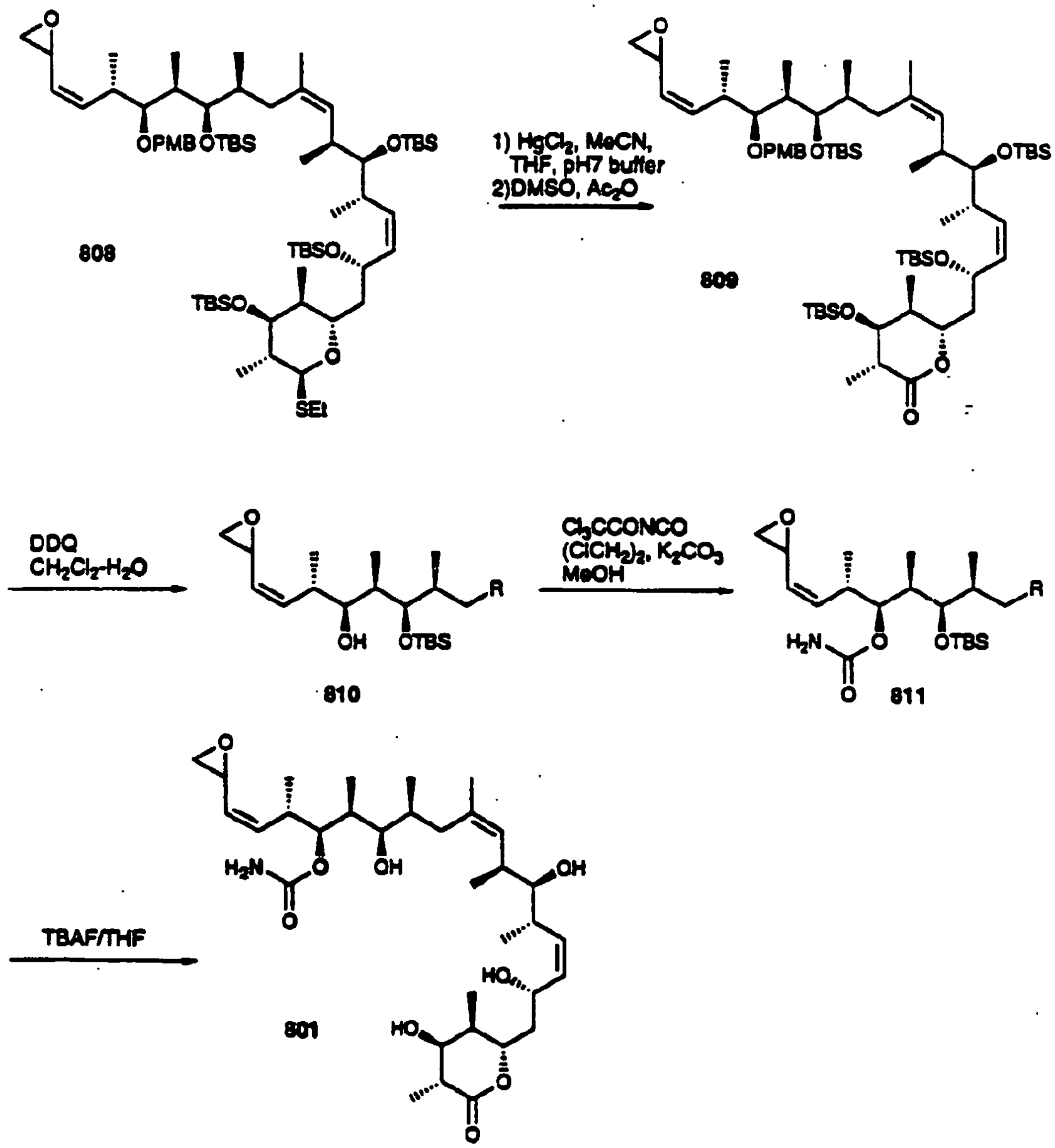

OPMB
OTBS
OTBS
808
TBSO
TBSO
SEt
1) HgCl$_2$, MeCN, THF, pH7 buffer
2)DMSO, Ac$_2$O
809
DDQ
CH$_2$Cl$_2$-H$_2$O
OH
R
810
Cl$_3$CCONCO
(ClCH$_2$)$_2$, K$_2$CO$_3$
MeOH
H$_2$N
811
TBAF/THF
HO
801

Figure 29

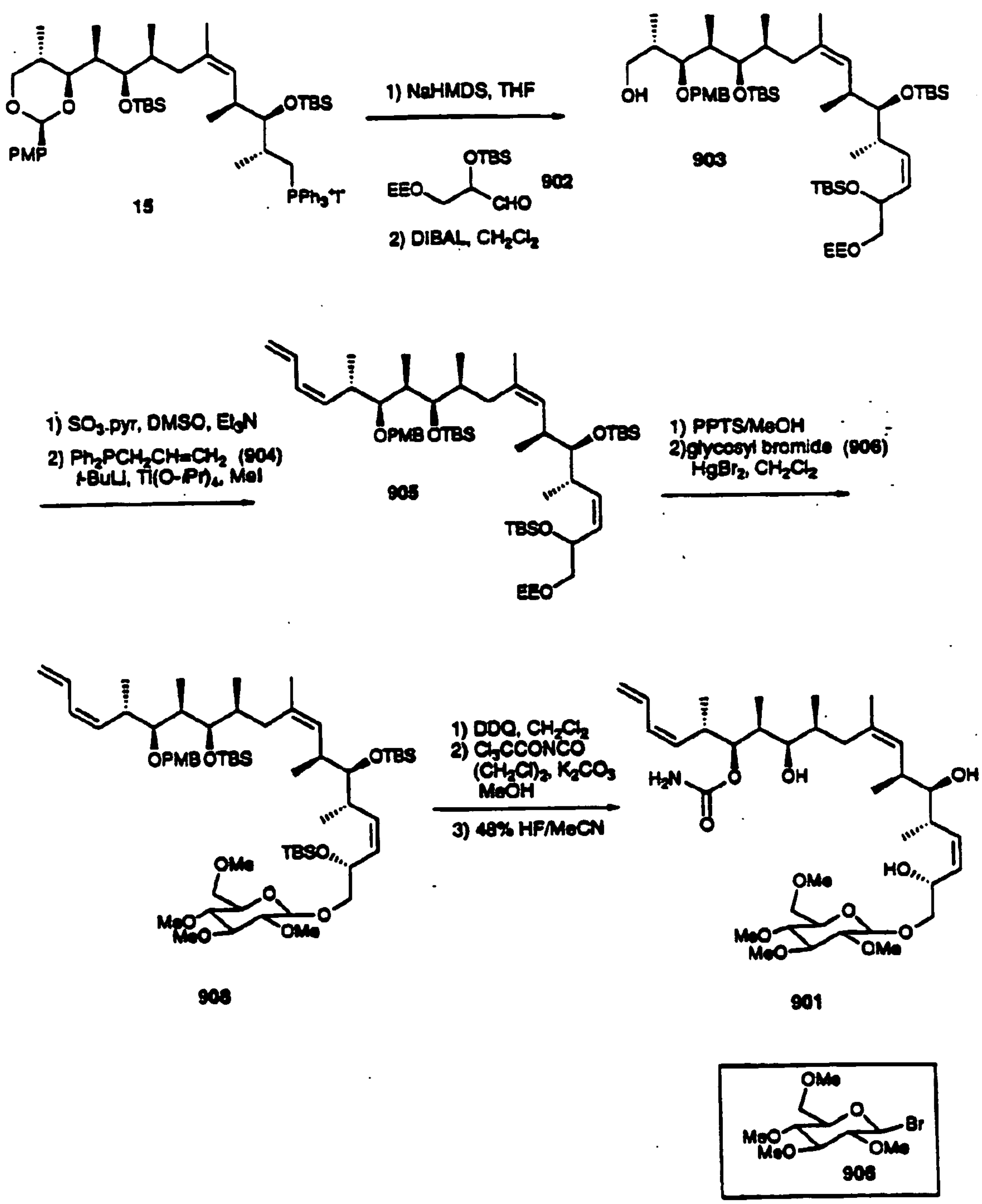

15
1) NaHMDS, THF
902
2) DIBAL, CH2Cl2
903
1) SO3.pyr, DMSO, Et3N
2) Ph2PCH2CH=CH2 (904)
t-BuLi, Ti(O-iPr)4, MeI
905
1) PPTS/MeOH
2)glycosyl bromide (906)
HgBr2, CH2Cl2
908
1) DDQ, CH2Cl2
2) Cl3CCONCO
(CH2Cl)2, K2CO3
MeOH
3) 48% HF/MeCN
901
906

Figure 30

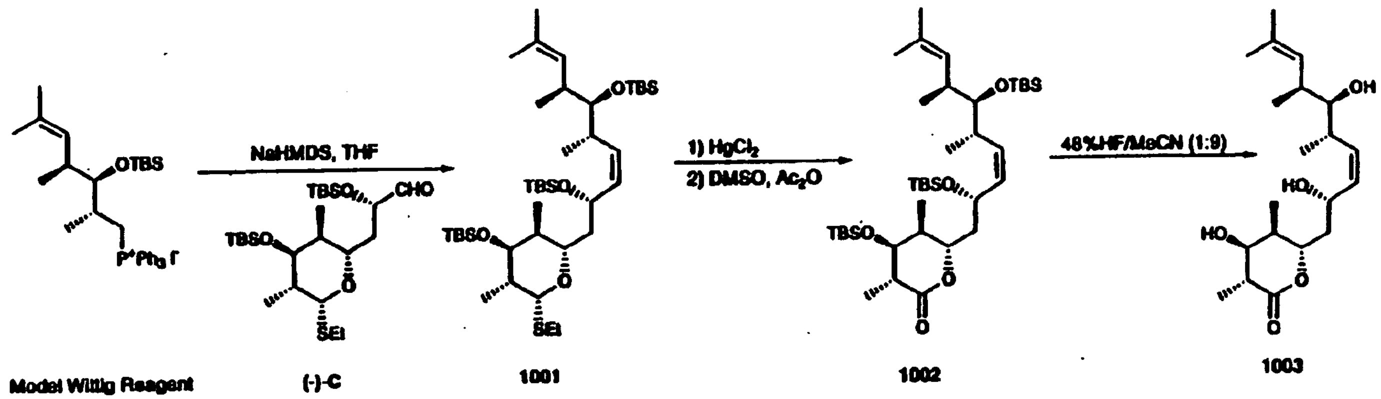


Figure 31

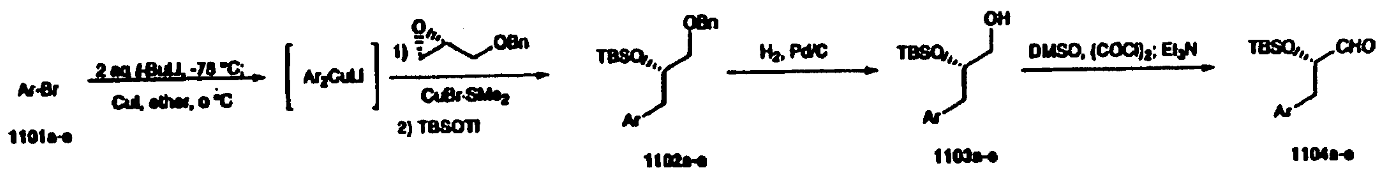
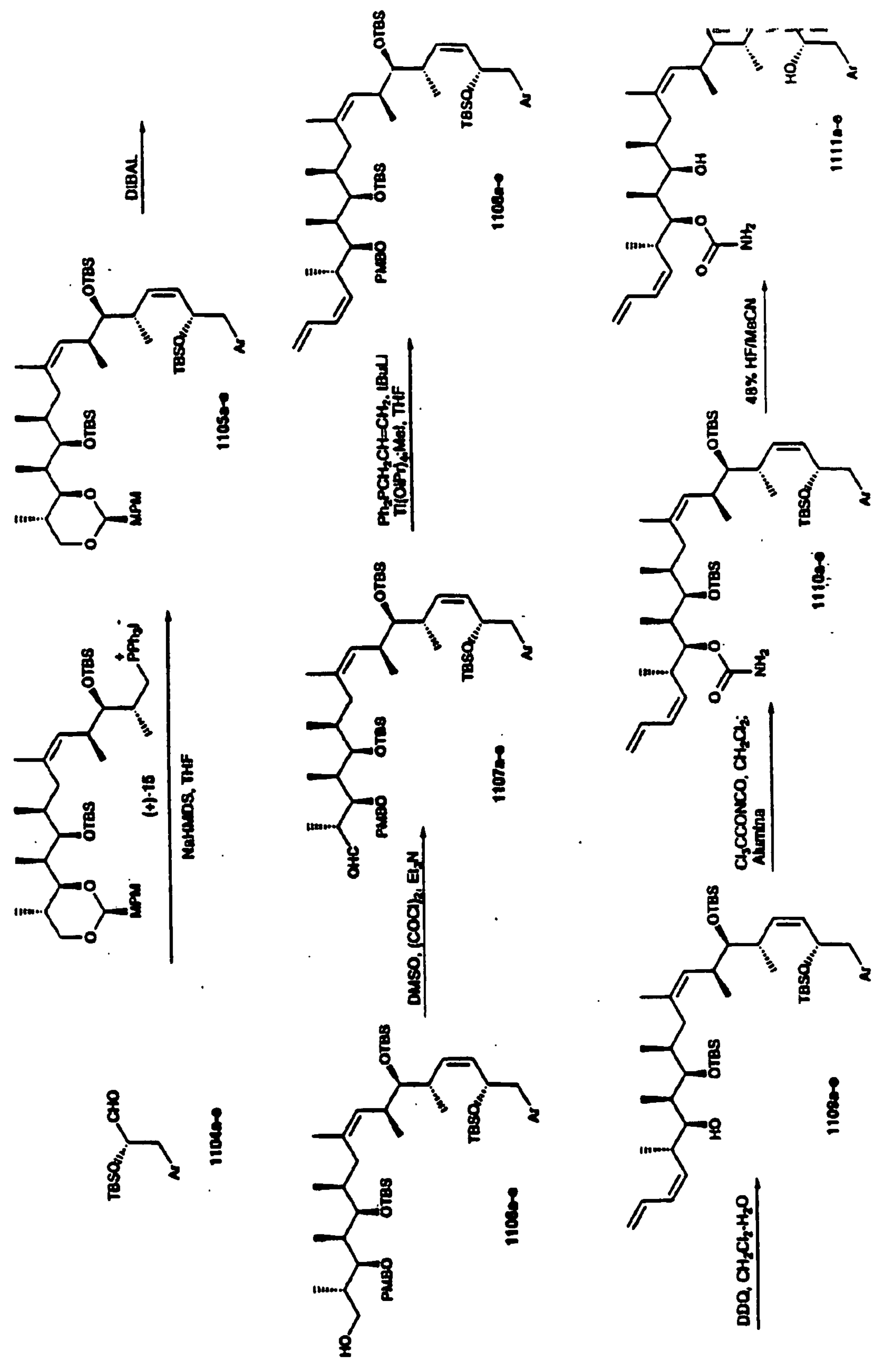


Figure 32



1104a-e
(+)-15
NaHMDS, THF
1105a-e
DIBAL
1106a-e
DMSO, (COCl)$_2$, Et$_3$N
1107a-e
Ph$_2$PCH$_2$CH=CH$_2$, tBuLi
Ti(OiPr)$_4$;MeI, THF
1108a-e
DDQ, CH$_2$Cl$_2$-H$_2$O
1109a-e
Cl$_3$CCONCO, CH$_2$Cl$_2$;
Alumina
1110a-e
48% HF/MeCN
1111a-e

Figure 33

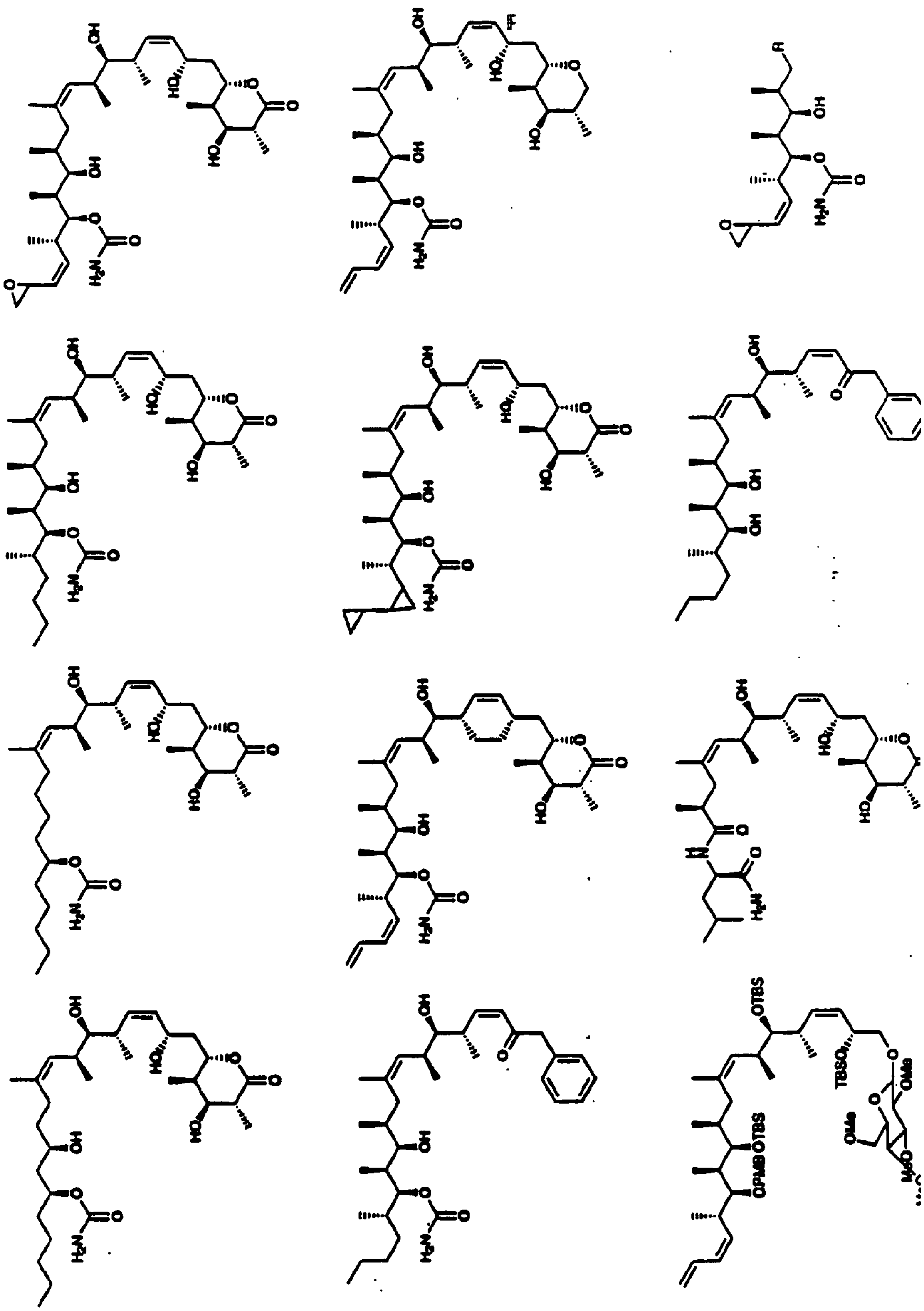


Figure 34

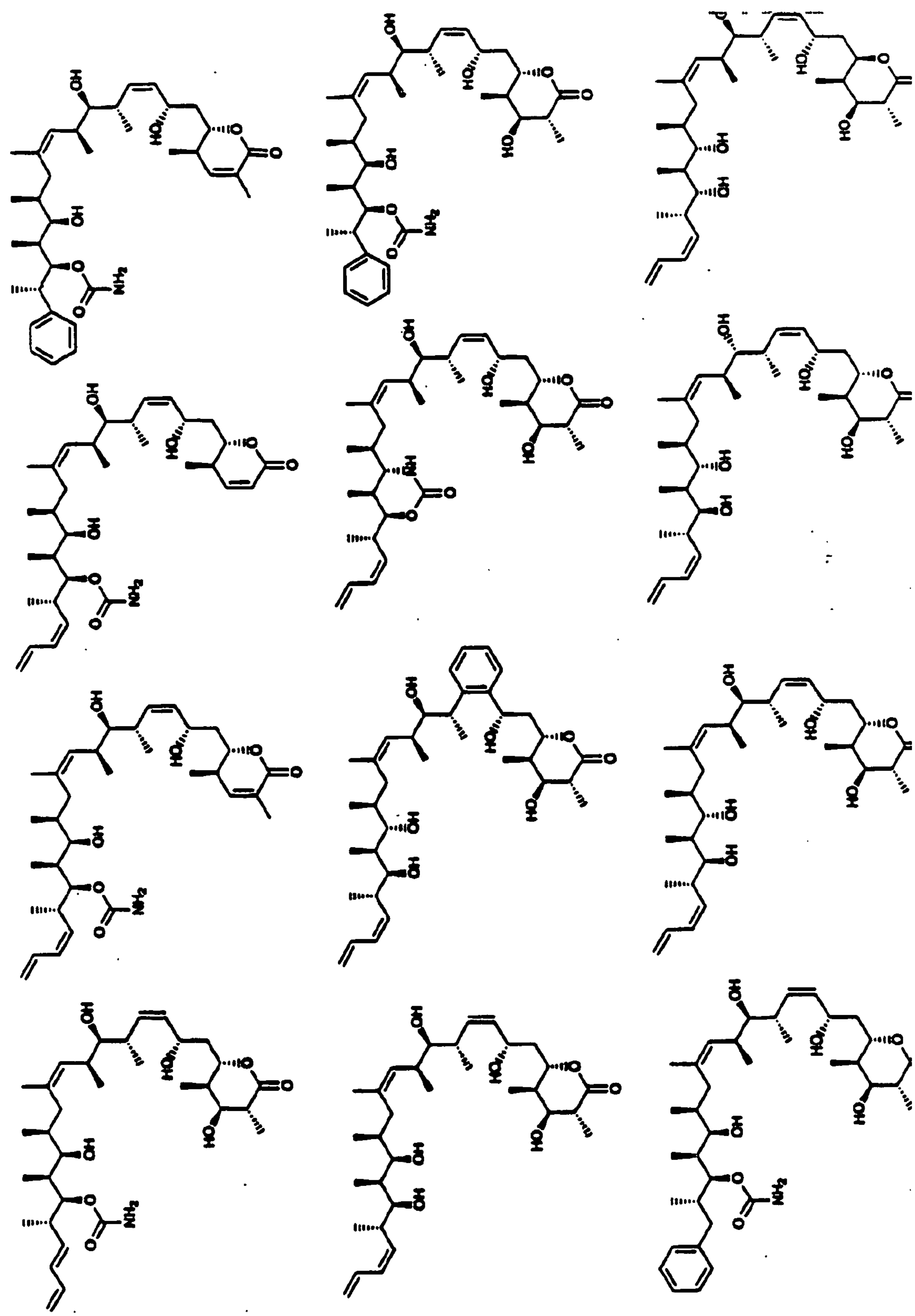
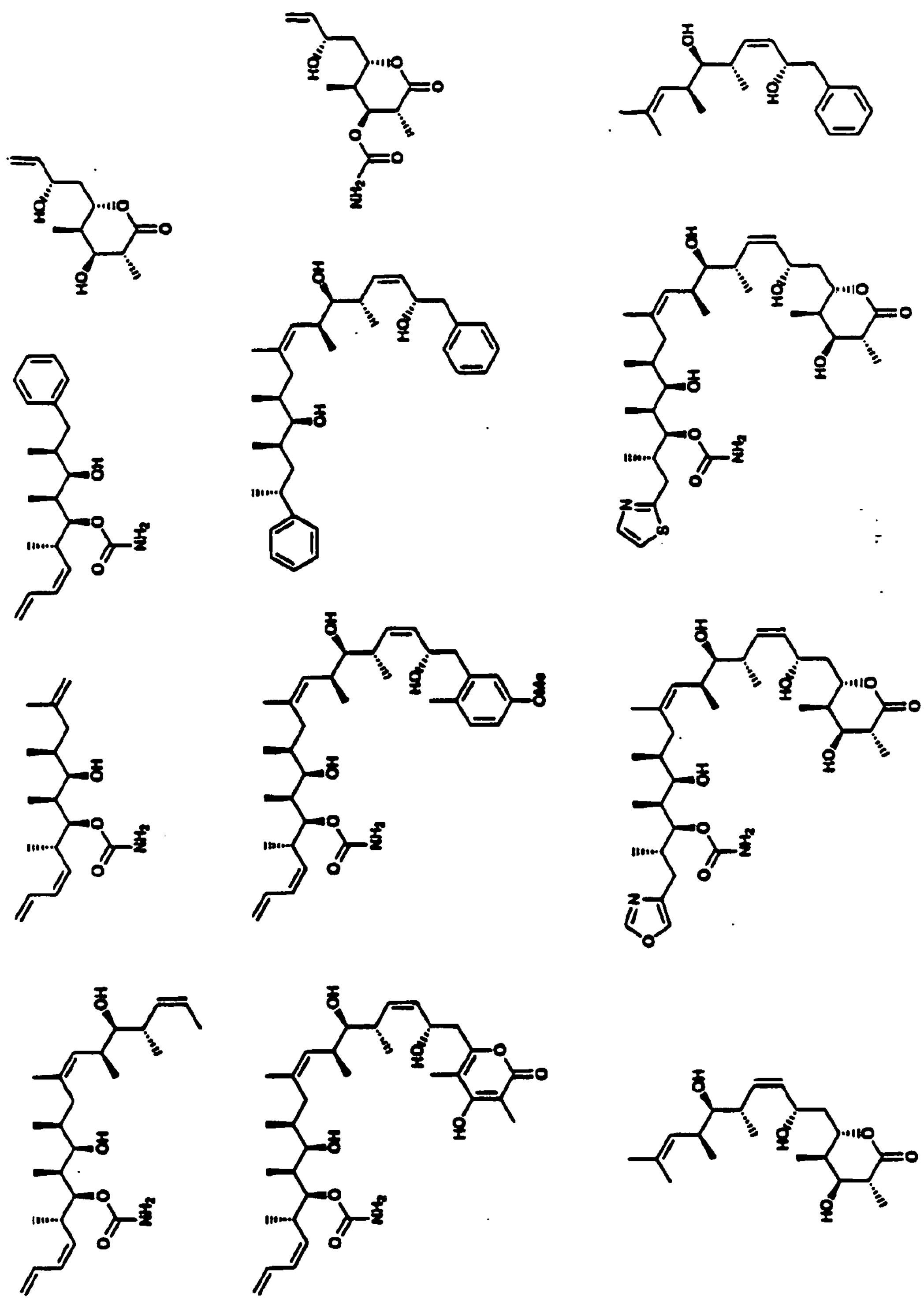


Figure 35



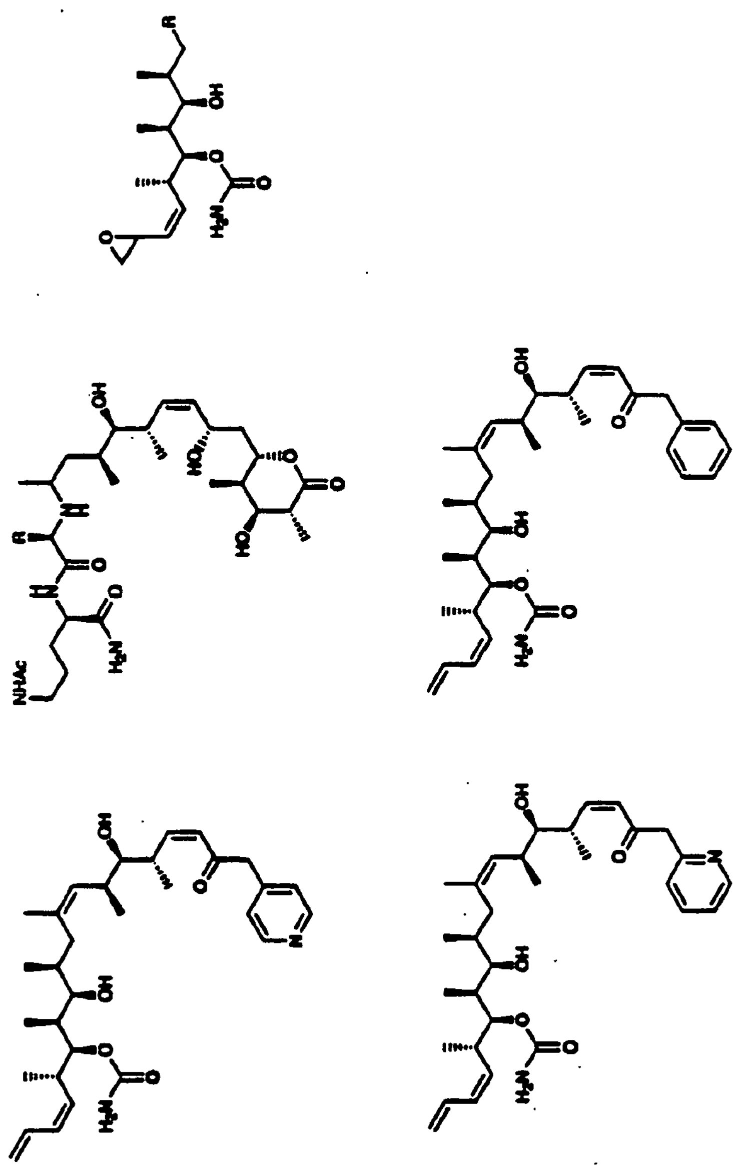


Figure 36

Figure 37

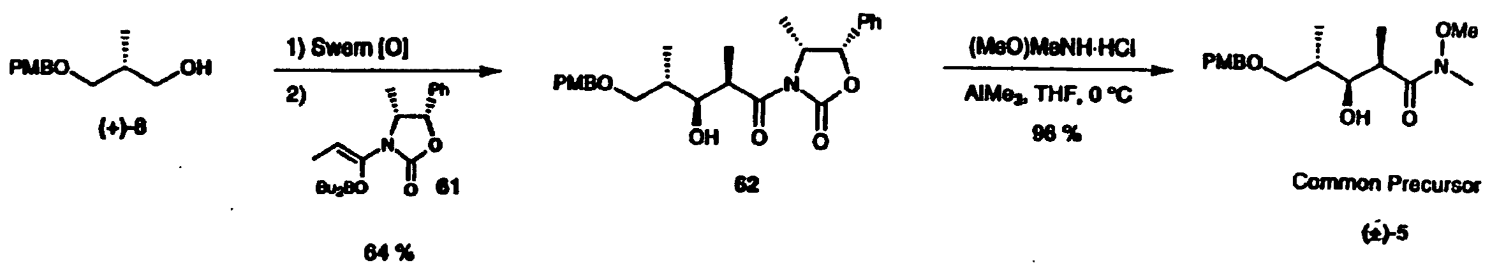

PMBO
OH
(+)-6
1) Swern [O]
2)
Ph
N
O
Bu_2BO
O
61
64 %
PMBO
OH
O
N
O
O
Ph
62
(MeO)MeNH·HCl
$AlMe_3$, THF, 0 °C
96 %
PMBO
OH
O
N
OMe
Common Precursor
(±)-5

Figure 38

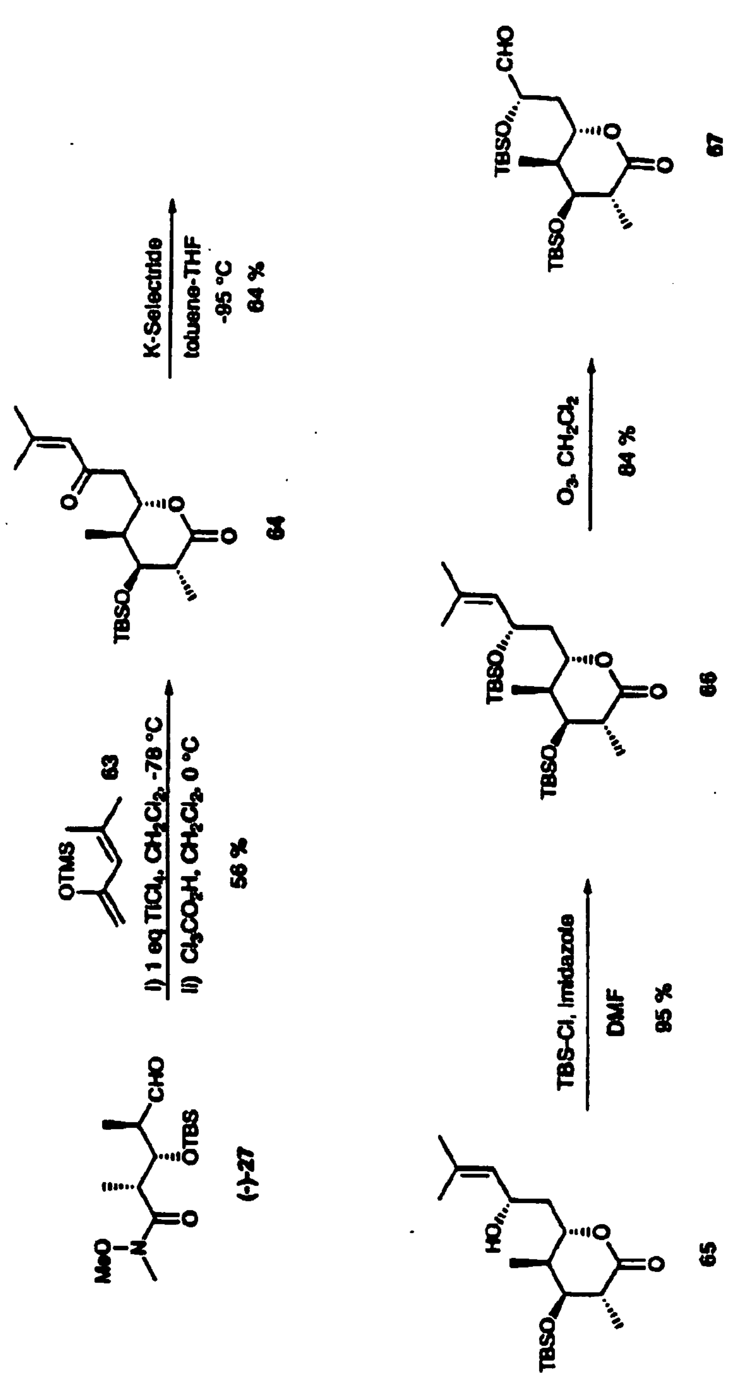

MeO
CHO
OTBS
(-)-27
OTMS
63
i) 1 eq TiCl$_4$, CH$_2$Cl$_2$, -78 °C
ii) Cl$_3$CO$_2$H, CH$_2$Cl$_2$, 0 °C
56 %
TBSO
64
K-Selectride
toluene-THF
-95 °C
64 %
HO
65
TBS-Cl, imidazole
DMF
95 %
66
O$_3$, CH$_2$Cl$_2$
84 %
67

Figure 39

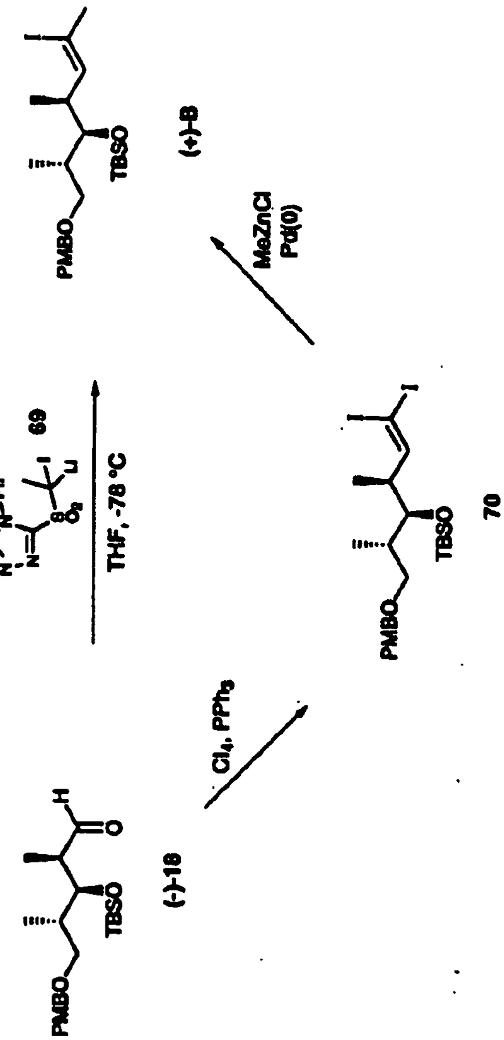
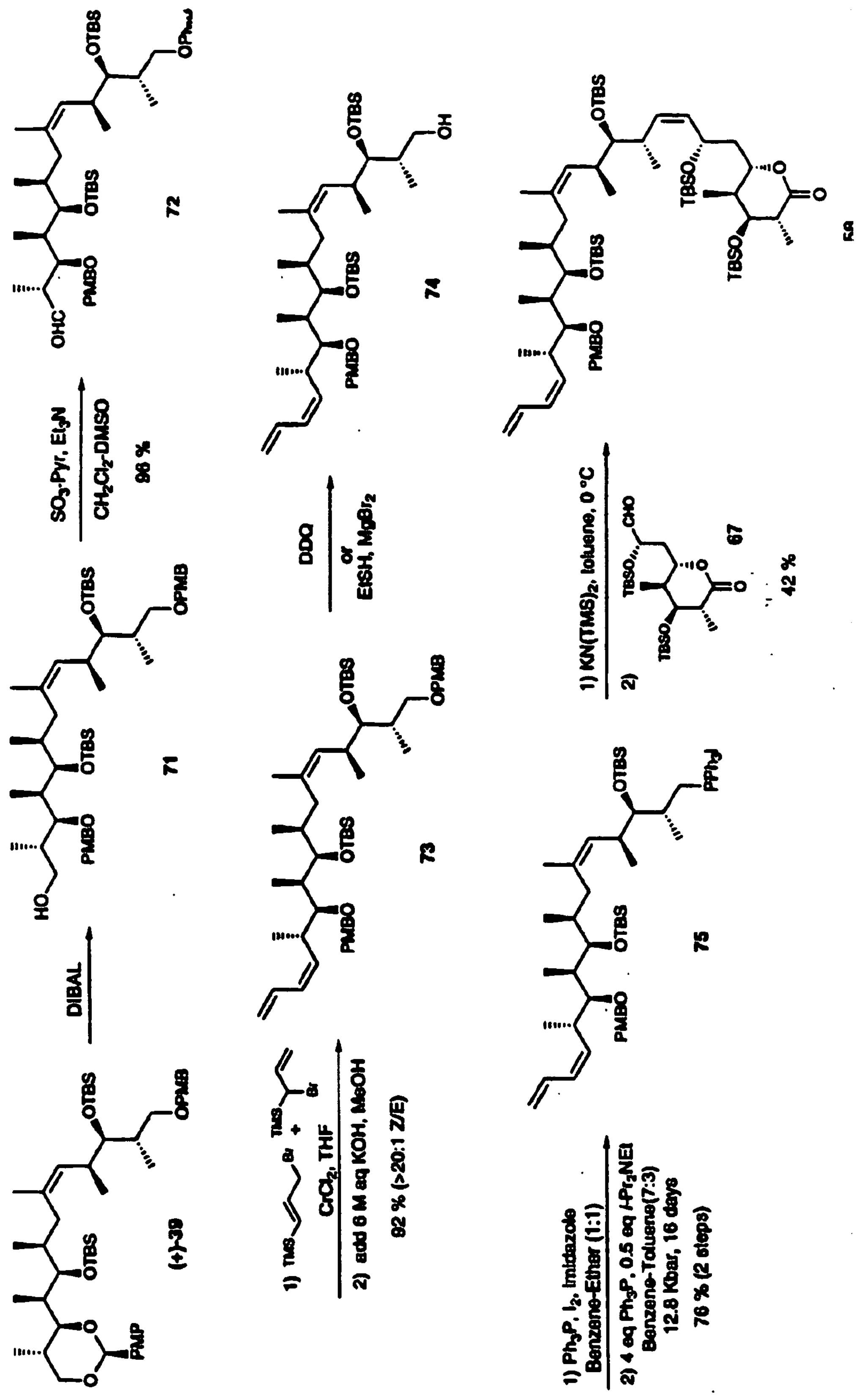
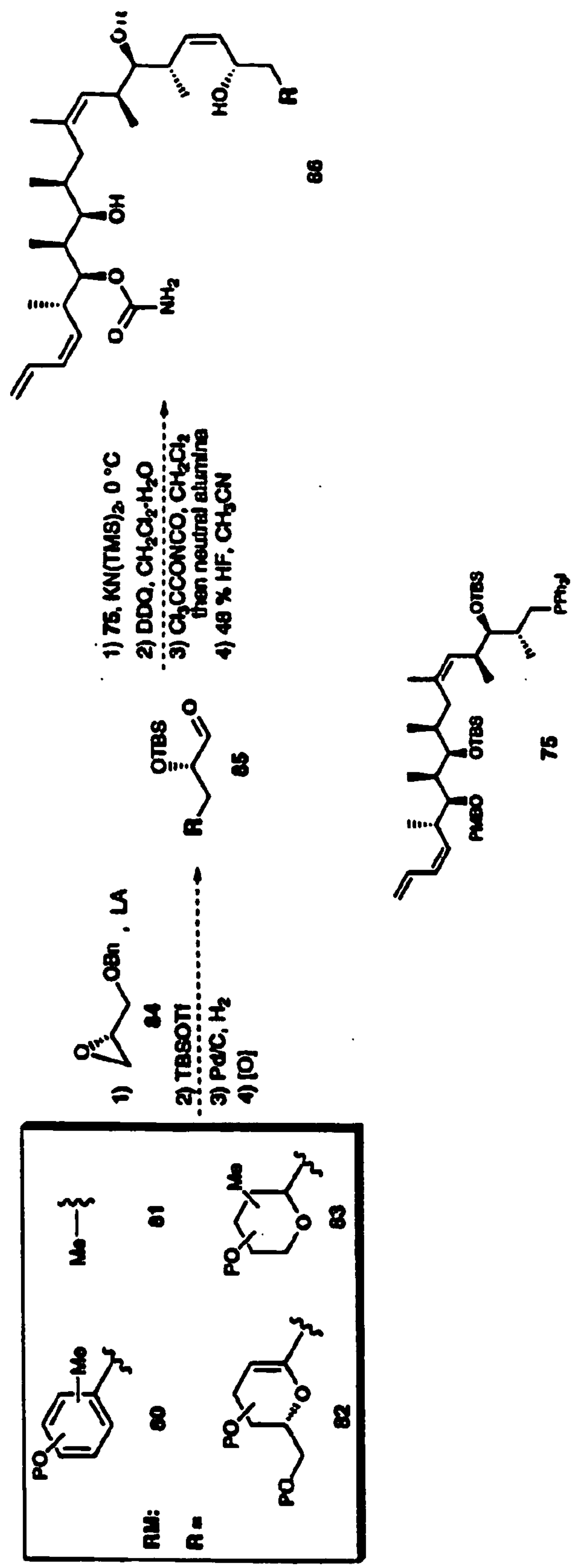


Figure 40



35/57

Figure 41



1) 84, LA
2) TBSOTf
3) Pd/C, H2
4) [O]
1) 75, KN(TMS)2, 0 °C
2) DDQ, CH2Cl2-H2O
3) Cl3CCONCO, CH2Cl2 then neutral alumina
4) 48 % HF, CH3CN
RM:
R =
80
81
82
83
84
85
86
75

Figure 42

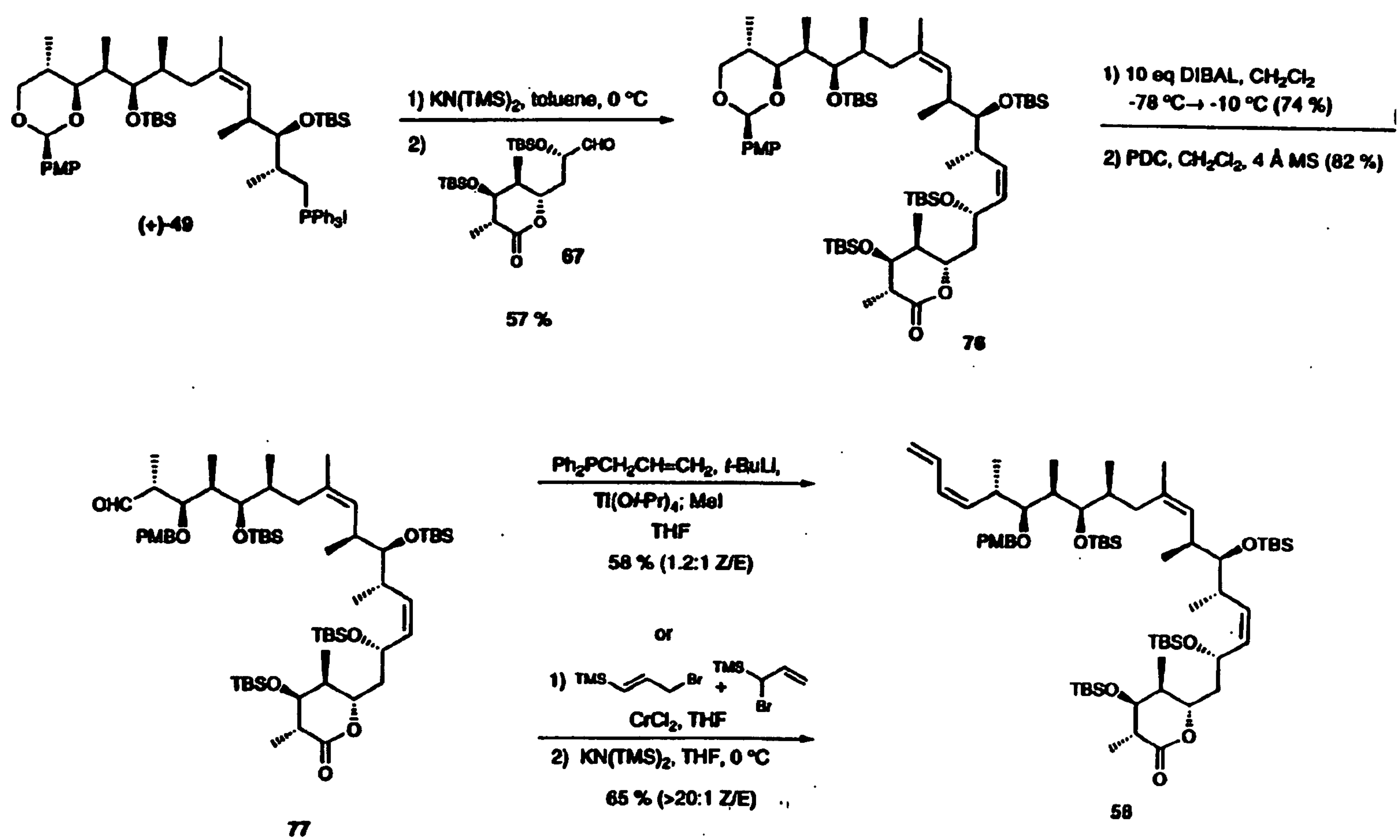

(+)-49
1) KN(TMS)$_2$, toluene, 0 °C
2)
67
57 %
76
1) 10 eq DIBAL, CH$_2$Cl$_2$
-78 °C→ -10 °C (74 %)
2) PDC, CH$_2$Cl$_2$, 4 Å MS (82 %)
77
Ph$_2$PCH$_2$CH=CH$_2$, t-BuLi,
Ti(O-i-Pr)$_4$; MeI
THF
58 % (1.2:1 Z/E)
or
1) TMS
CrCl$_2$, THF
2) KN(TMS)$_2$, THF, 0 °C
65 % (>20:1 Z/E)
58

Figure 43

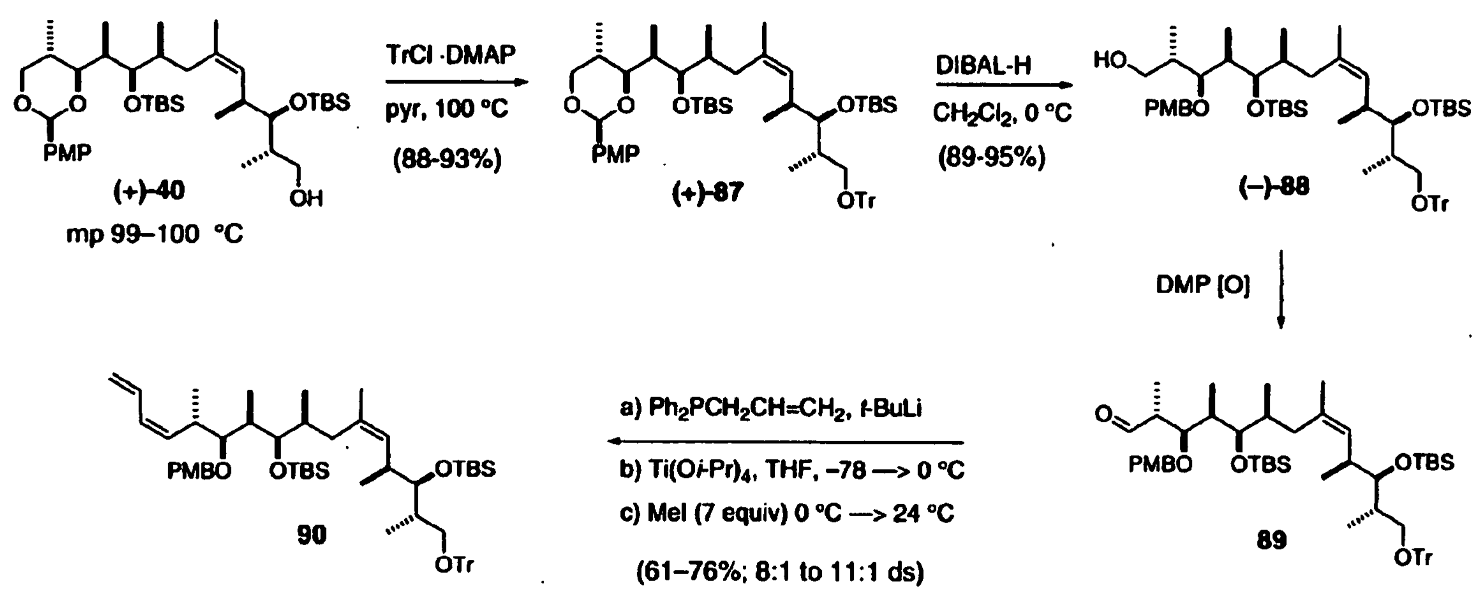

OTBS
PMP
(+)-40
OH
mp 99–100 °C
TrCl ·DMAP
pyr, 100 °C
(88-93%)
(+)-87
OTr
DIBAL-H
CH_2Cl_2, 0 °C
(89-95%)
HO
PMBO
(–)-88
DMP [O]
89
a) $Ph_2PCH_2CH{=}CH_2$, t-BuLi
b) $Ti(Oi\text{-}Pr)_4$, THF, –78 —> 0 °C
c) MeI (7 equiv) 0 °C —> 24 °C
(61–76%; 8:1 to 11:1 ds)
90

Figure 44

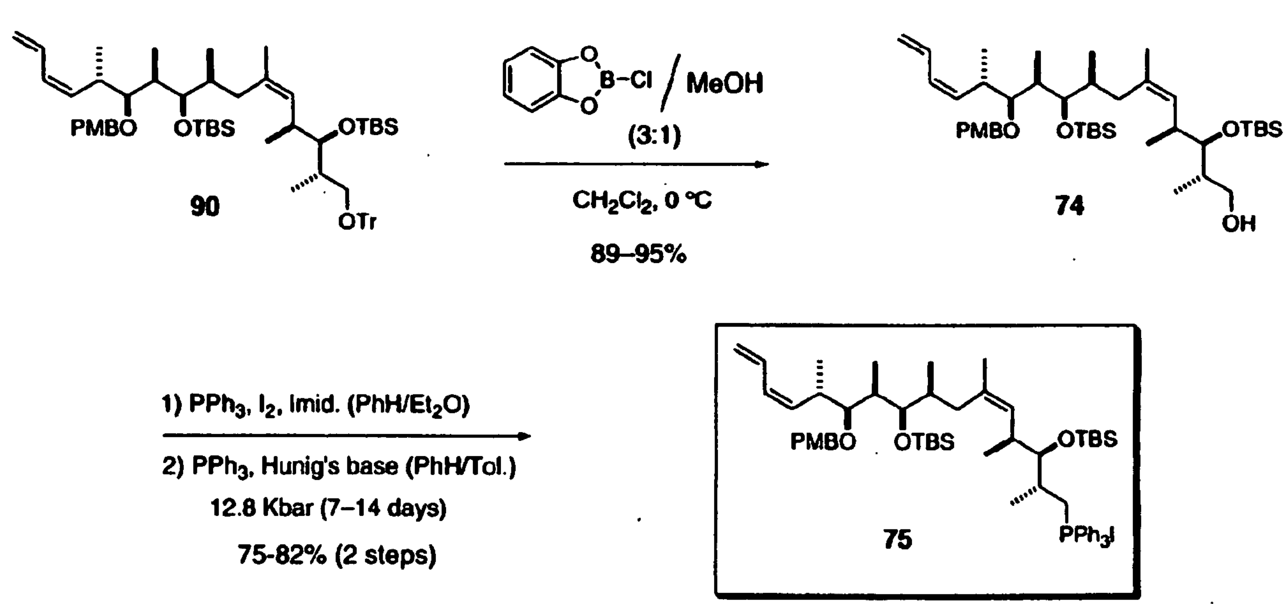

PMBO
OTBS
OTBS
90
OTr
B–Cl
MeOH
(3:1)
CH2Cl2, 0 °C
89–95%
PMBO
OTBS
OTBS
74
OH
1) PPh3, I2, Imid. (PhH/Et2O)
2) PPh3, Hunig's base (PhH/Tol.)
12.8 Kbar (7–14 days)
75-82% (2 steps)
PMBO
OTBS
OTBS
75
PPh3I

Figure 45

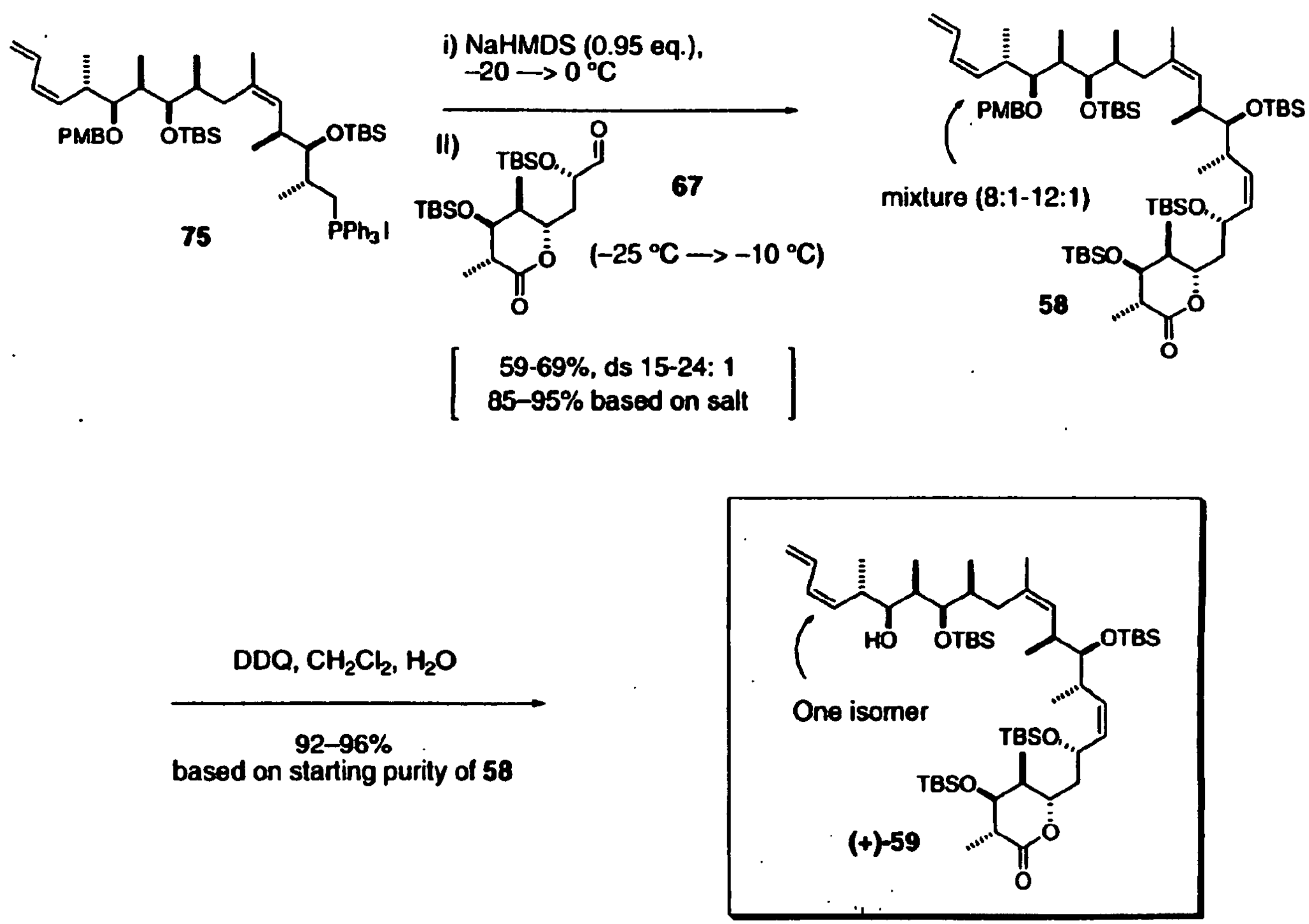

i) NaHMDS (0.95 eq.), –20 —> 0 °C
ii)
67
(–25 °C —> –10 °C)
59-69%, ds 15-24: 1
85–95% based on salt
75
PMBO
OTBS
PPh3I
TBSO
mixture (8:1-12:1)
58
DDQ, CH2Cl2, H2O
92–96%
based on starting purity of 58
HO
One isomer
(+)-59

Figure 46

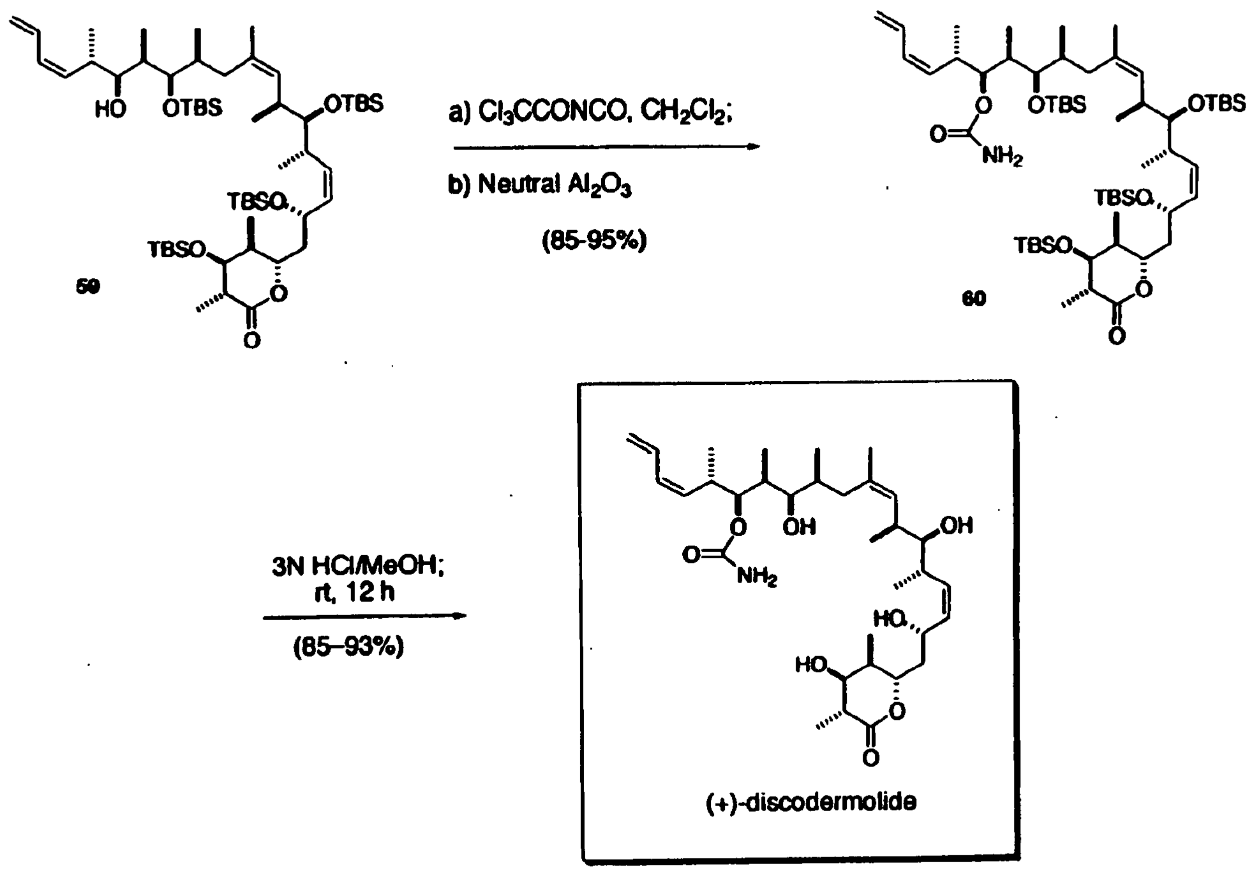

HO
OTBS
OTBS
TBSO
TBSO
59
a) $Cl_3CCONCO$, CH_2Cl_2;
b) Neutral Al_2O_3
(85-95%)
O
NH2
OTBS
OTBS
TBSO
TBSO
60
3N HCl/MeOH;
rt, 12 h
(85–93%)
OH
OH
HO
HO
NH2
(+)-discodermolide

Figure 47

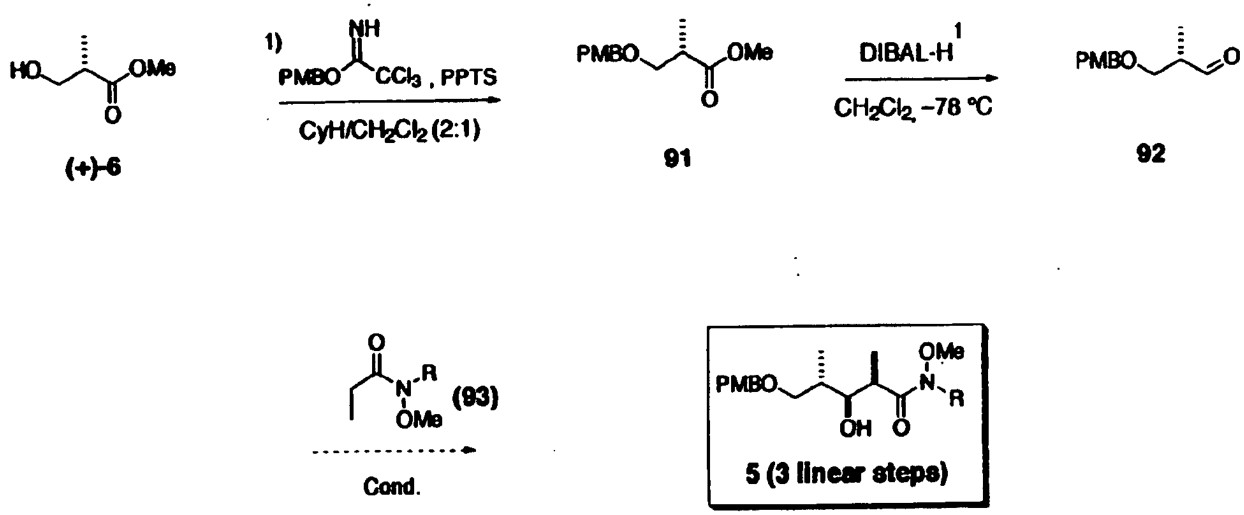

HO
OMe
O
(+)-6
1)
NH
PMBO
CCl_3 , PPTS
CyH/CH_2Cl_2 (2:1)
PMBO
OMe
O
91
DIBAL-H
1
CH_2Cl_2, −78 °C
PMBO
O
92
O
N
R
OMe
(93)
Cond.
PMBO
OMe
N
R
OH
O
5 (3 linear steps)

Figure 48

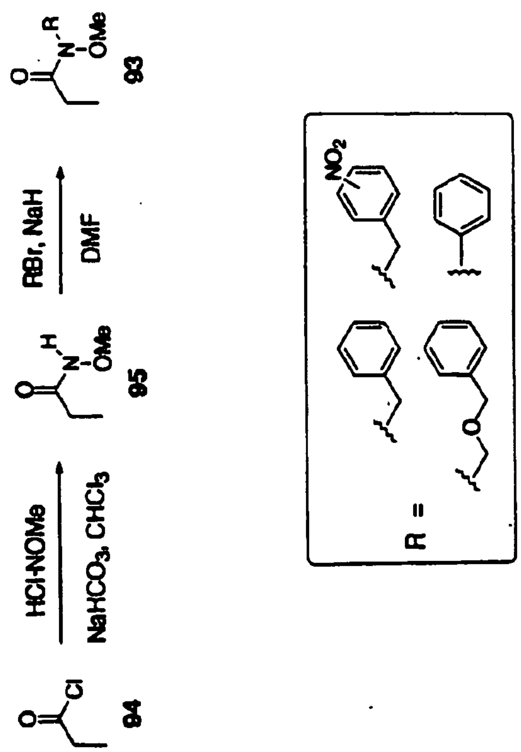


Figure 49

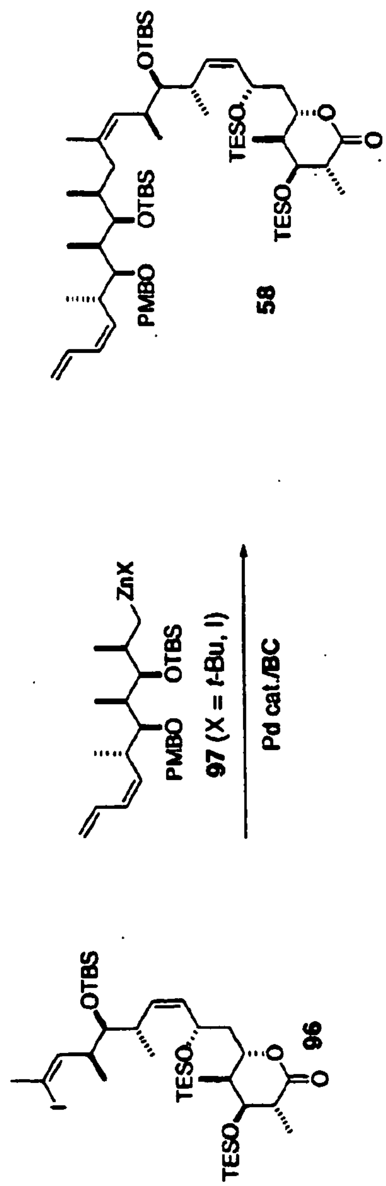

OTBS
TESO
TESO
96
PMBO
OTBS
ZnX
97 (X = t-Bu, I)
Pd cat./BC
PMBO
OTBS
OTBS
TESO
TESO
58

Figure 50

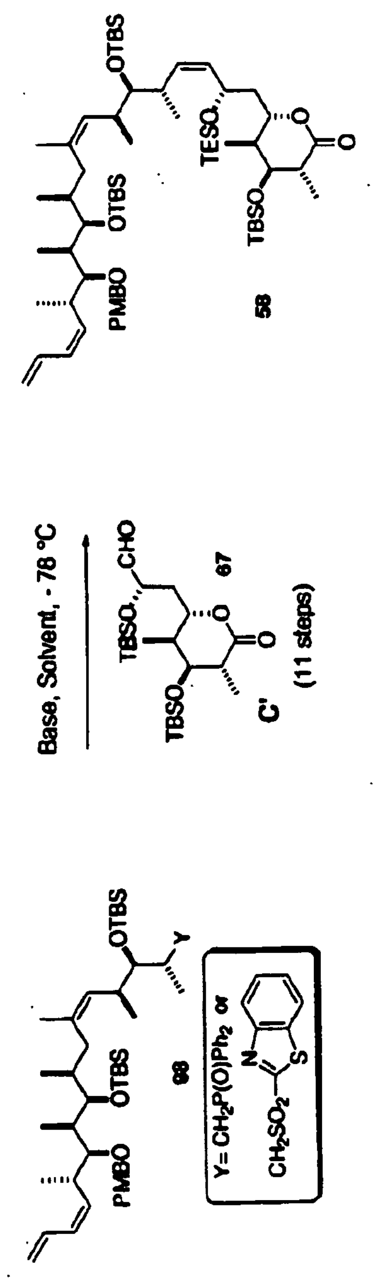
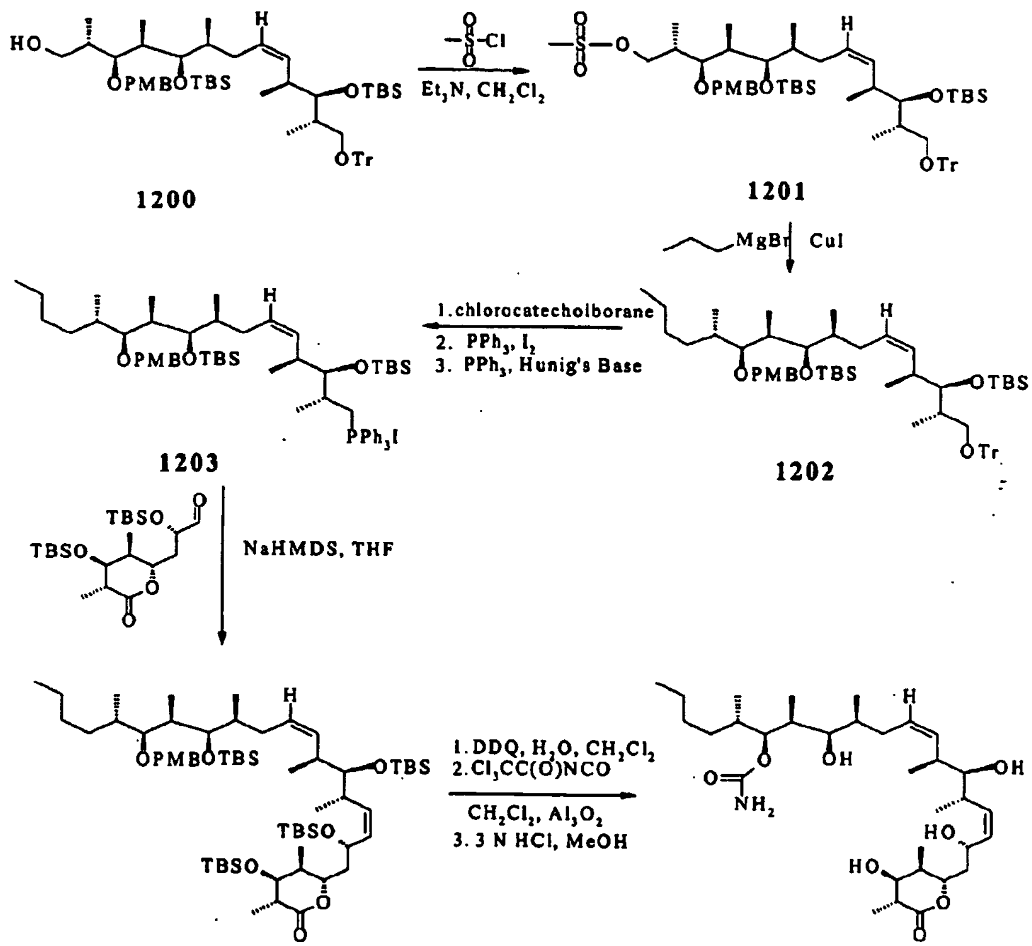

PMBO
OTBS
OTBS
Y
98
Y= CH2P(O)Ph2 or
CH2SO2
N
S
Base, Solvent, - 78 °C
TBSO
TBSO
CHO
67
C'
(11 steps)
TESO
TBSO
58

Figure 51



1200 1201 1202 1203 1204 1205

Figure 52

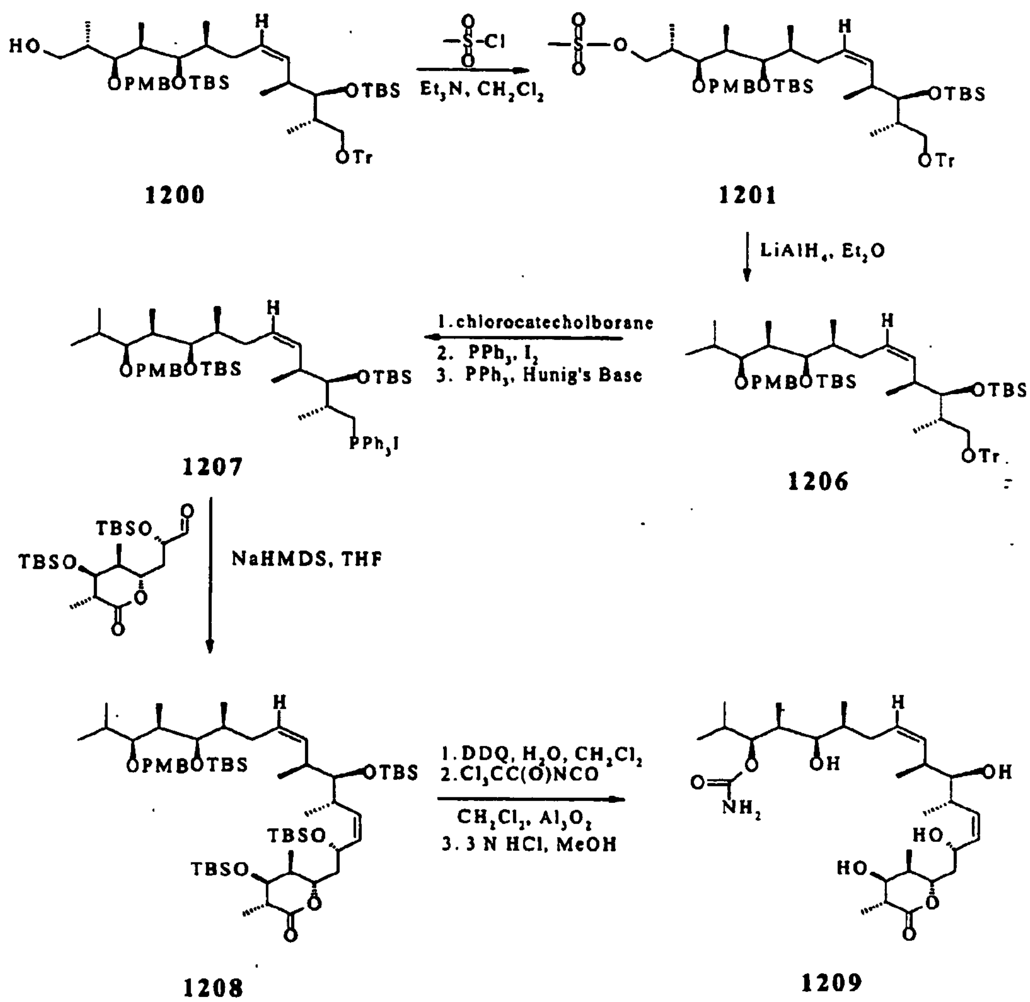
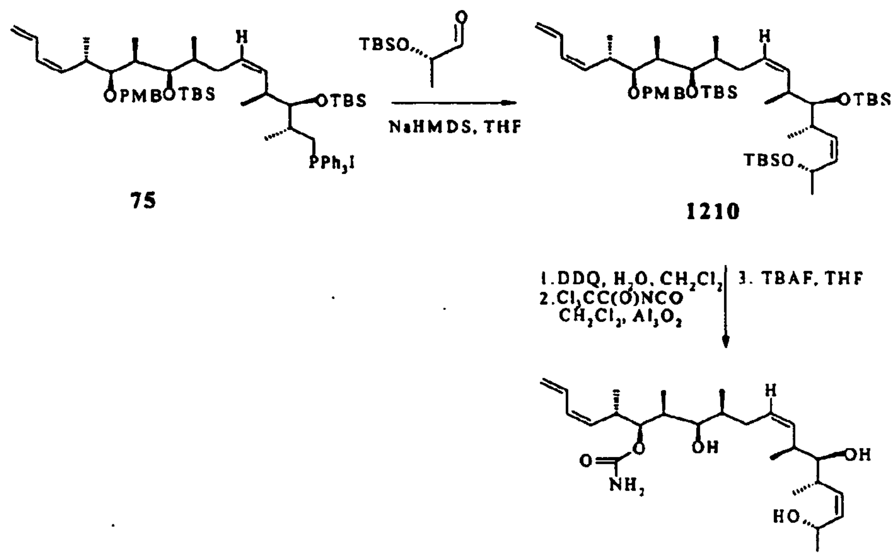

HO
OPMB OTBS
OTBS
OTr
Et$_3$N, CH$_2$Cl$_2$
1200
1201
LiAlH$_4$, Et$_2$O
1. chlorocatecholborane
2. PPh$_3$, I$_2$
3. PPh$_3$, Hunig's Base
PPh$_3$I
1207
1206
TBSO
NaHMDS, THF
1. DDQ, H$_2$O, CH$_2$Cl$_2$
2. Cl$_3$CC(O)NCO
CH$_2$Cl$_2$, Al$_2$O$_3$
3. 3 N HCl, MeOH
NH$_2$
OH
HO
1208
1209

Figure 53



75

1210

1211

Figure 54

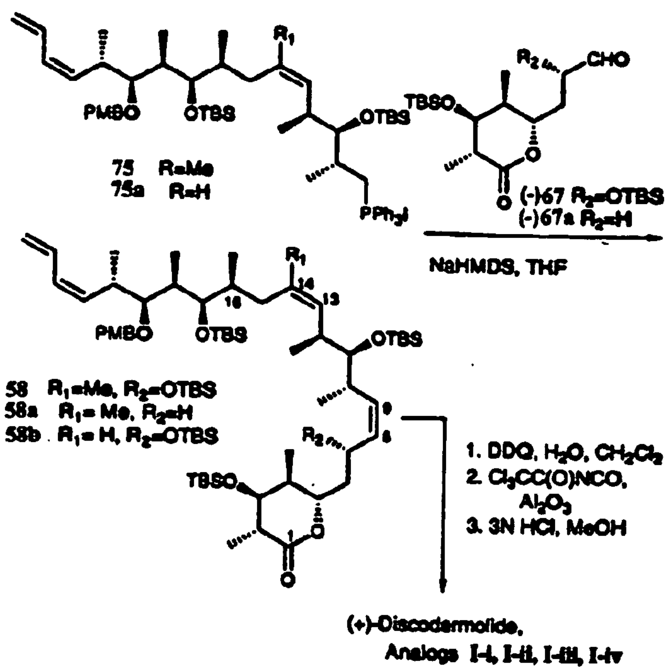


Figure 55

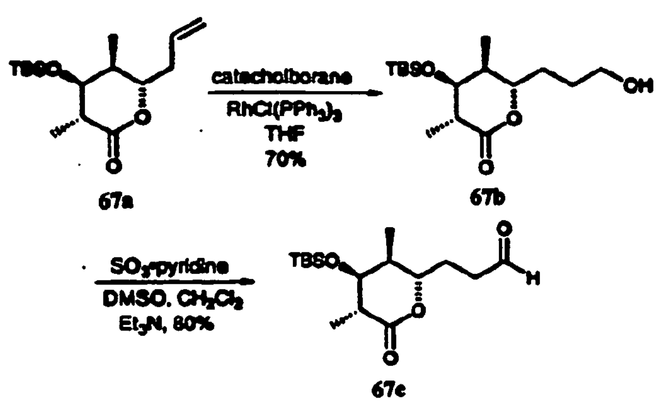


Figure 56

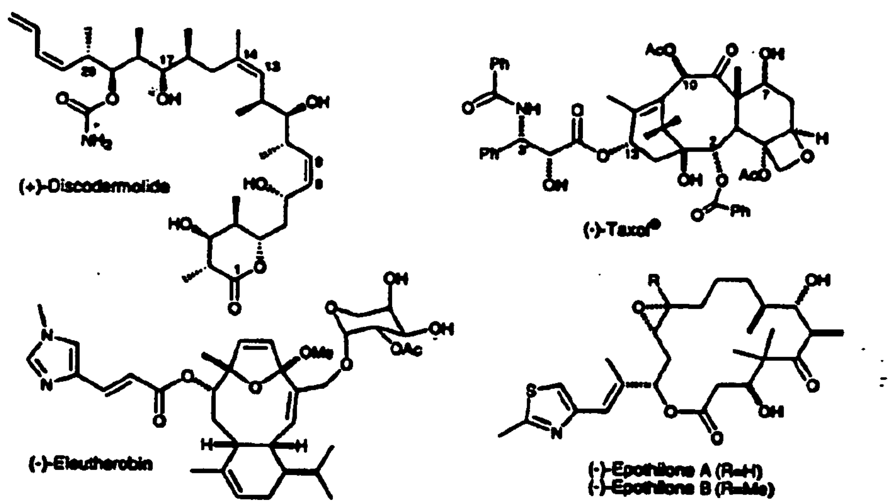


Figure 57

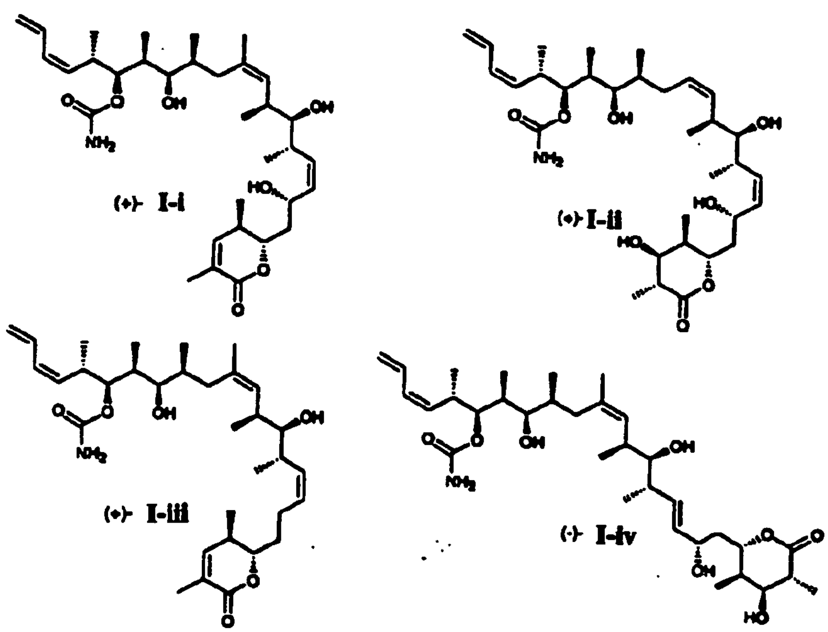


Figure 58

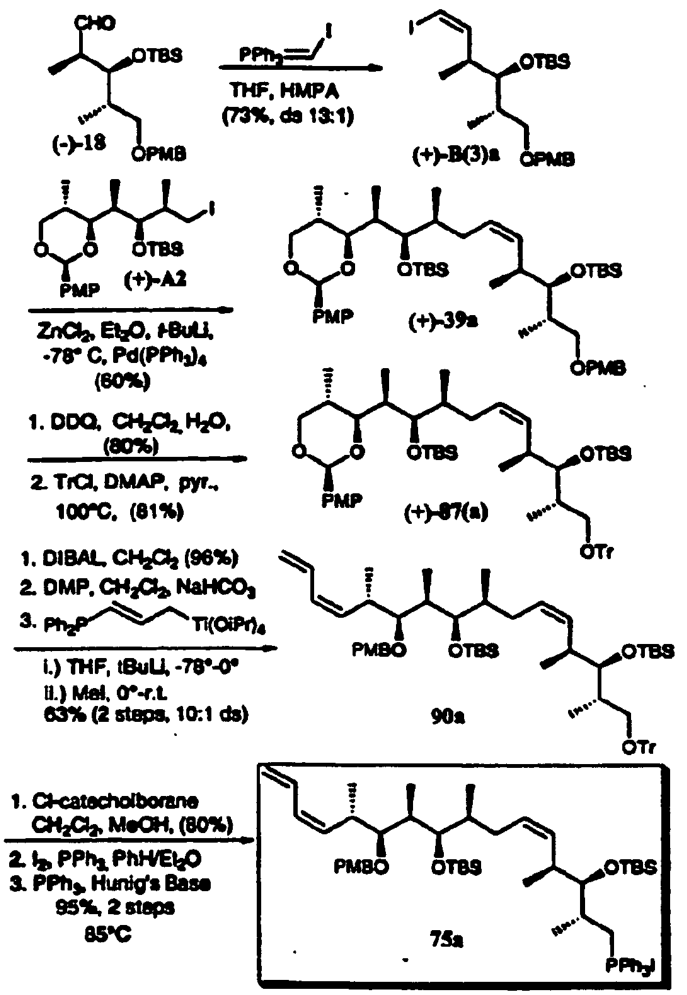


Figure 59

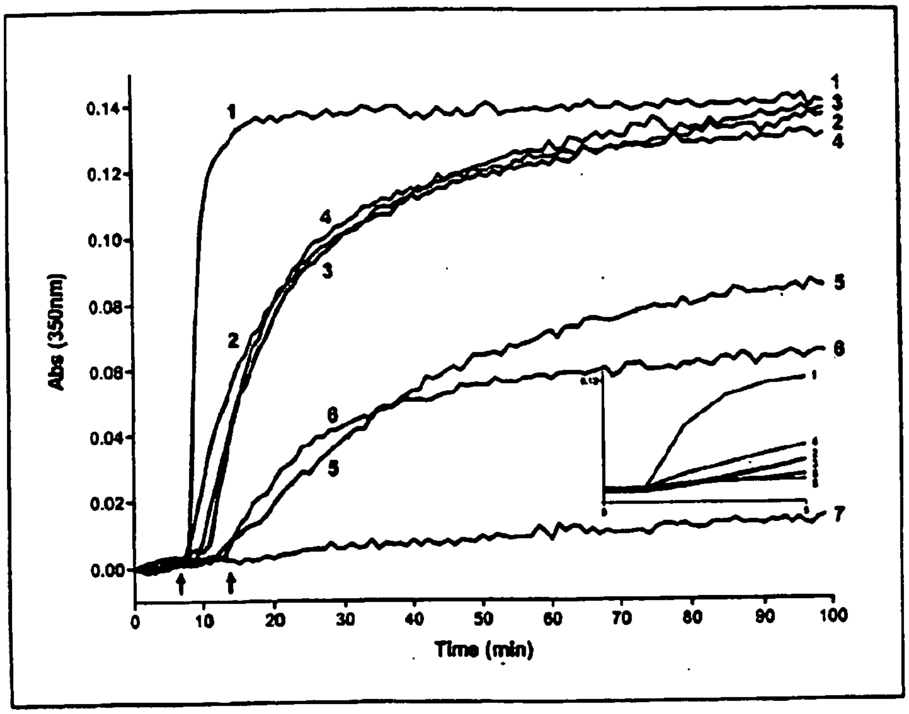

0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Abs (350nm)
0
10
20
30
40
50
60
70
80
90
100
Time (min)
1
2
3
4
5
6
7

Figure 60

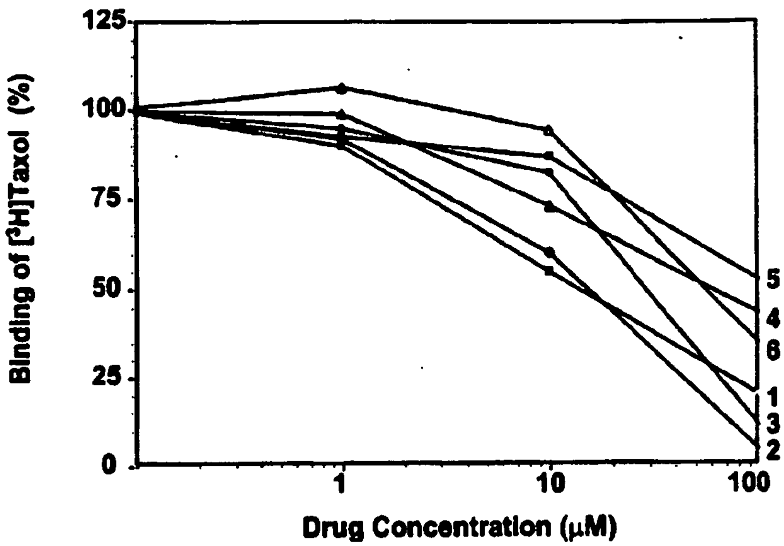

125
100
75
50
25
0
Binding of [³H]Taxol (%)
1
10
100
Drug Concentration (µM)
5
4
6
1
3
2

Figure 61

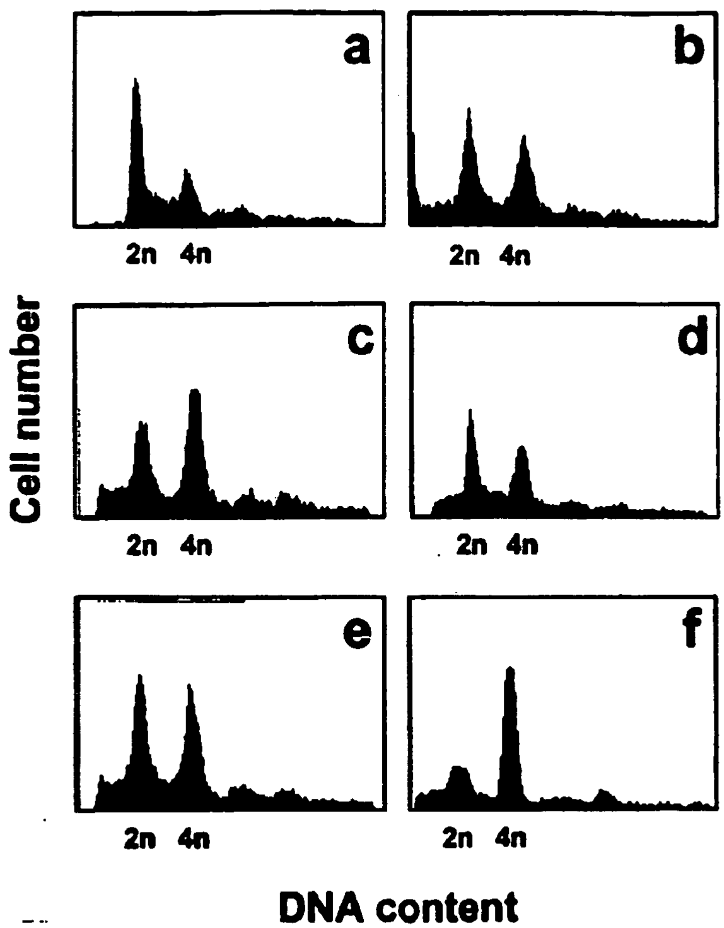

a
b
c
d
e
f
2n 4n
2n 4n
2n 4n
2n 4n
2n 4n
2n 4n
Cell number
DNA content

Figure 62

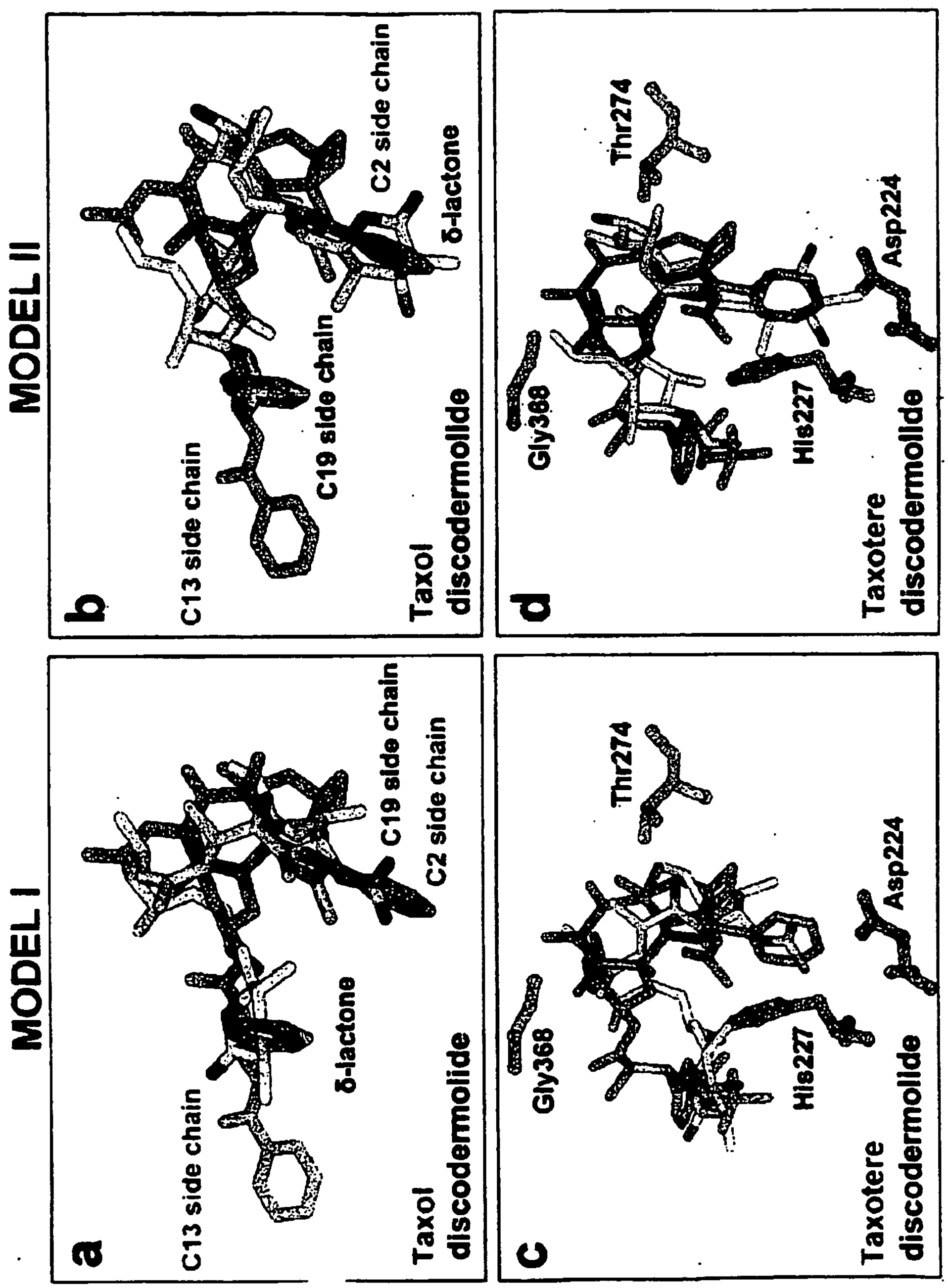

MODEL I
MODEL II
a
C13 side chain
δ-lactone
C19 side chain
C2 side chain
Taxol
discodermolide
b
C13 side chain
C19 side chain
δ-lactone
C2 side chain
Taxol
discodermolide
c
Gly368
Thr274
Asp224
His227
Taxotere
discodermolide
d
Gly368
Thr274
Asp224
His227
Taxotere
discodermolide

Figure 63

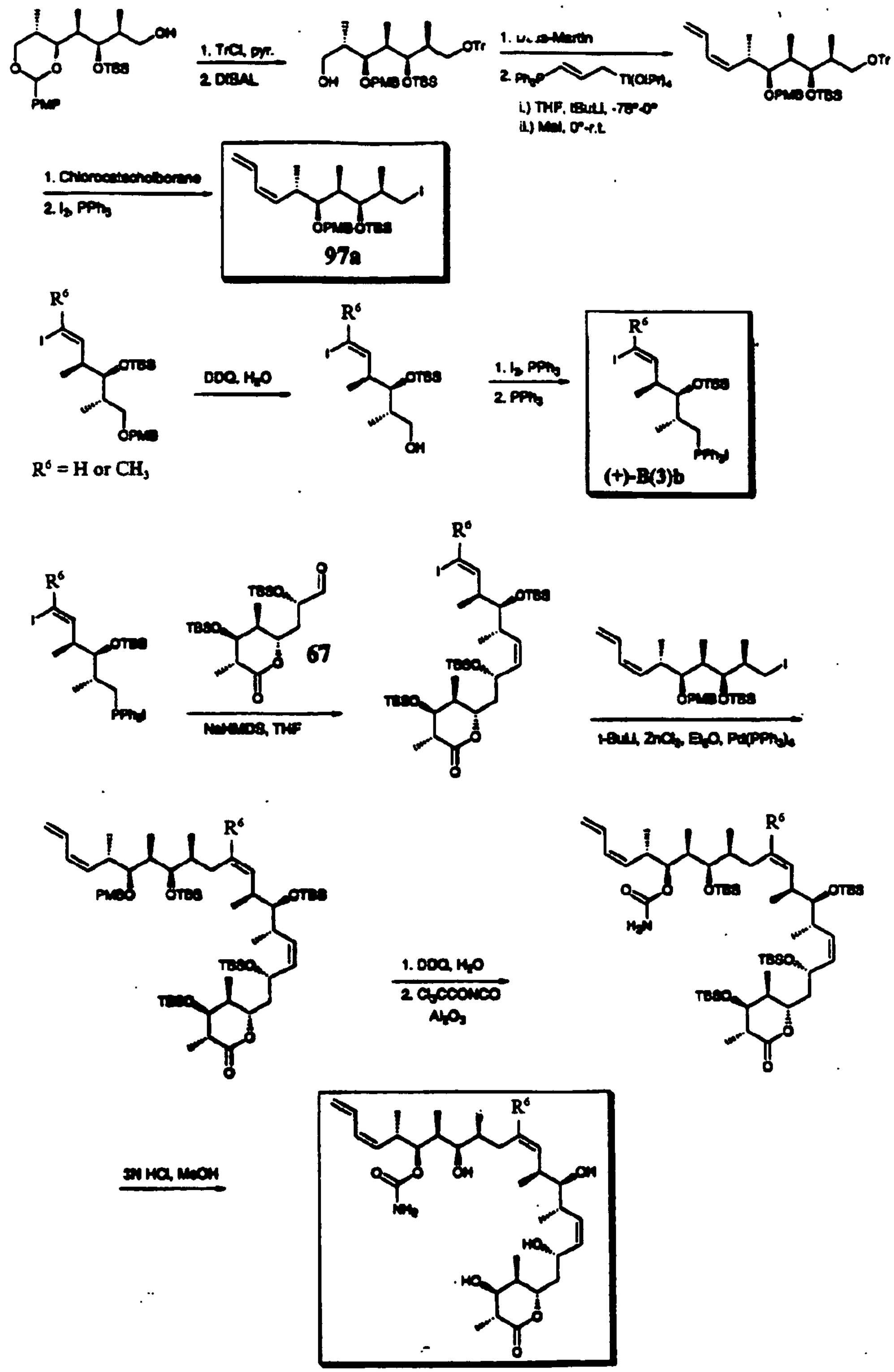
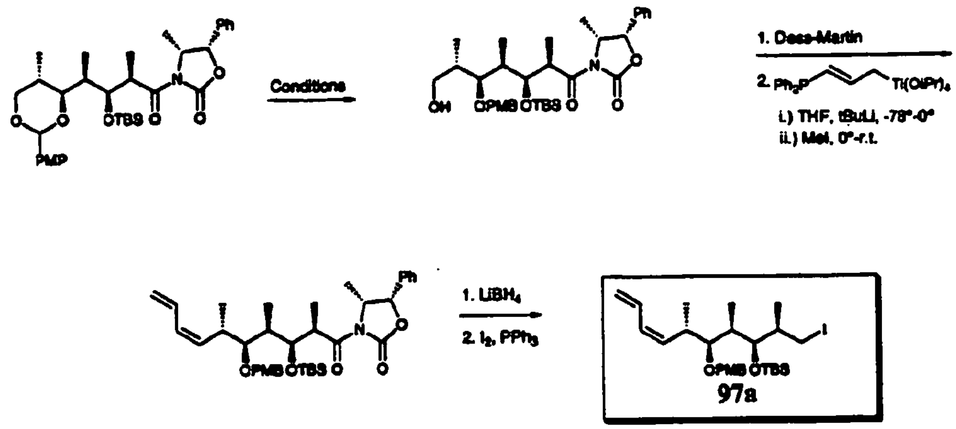

1. TrCl, pyr.
2. DIBAL
1. Dess-Martin
i.) THF, tBuLi, -78°-0°
ii.) MeI, 0°-r.t.
1. Chlorocatecholborane
2. I_2, PPh_3
97a
R^6 = H or CH_3
DDQ, H_2O
1. I_2, PPh_3
2. PPh_3
(+)-B(3)b
67
NaHMDS, THF
t-BuLi, $ZnCl_2$, Et_2O, $Pd(PPh_3)_4$
1. DDQ, H_2O
2. $Cl_3CCONCO$
Al_2O_3
3N HCl, MeOH

Figure 64


Ph
PMP
OTBS
Conditions
OH
OPMB
1. Dess-Martin
2. Ph_2P Ti(OiPr)$_4$
i.) THF, tBuLi, -78°-0°
ii.) MeI, 0°-r.t.
1. $LiBH_4$
2. I_2, PPh_3
I
97a

INTERNATIONAL SEARCH REPORT	International application No. PCT/US02/24932

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/25; C07D 309/30
US CL : 514/460; 549/292

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/460; 549/292

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,010,099 (GUNASEKERA et al) 23 April 1991 (23.04.1991), column 2, lines 37-67, columns 3-4, lines 1-19, colum 7, line 40-column 9, line 68.	1-11, 13, 14, 18, 19
X --- Y	HUNG et al, Synthesis of Discodermolides Useful for Investigating Microtuble Binding and Stabilization, Journal of the American Chemical Society 1996, 118, pages 11054-11080, page 11055, column 1, compound 1a, page 11066, column 1, Table 2 and first full paragraph.	1-10, 13, 14, 18-20 --- 11
X	US 5,681,847 A (LONGLEY et al) 28 October 1997 (28.10.1997), column 1, lines 21-36, column 2, line 36-column 4, line 26, column 8, lines 29-45, column 10, lines 6-63.	1-11, 13, 14,18-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 06 December 2002 (06.12.2002)	Date of mailing of the international search report 03 JAN 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Paul A. Zucker Valerie Bell-Harris for Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/24932

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 12 and 15-17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/24932

Continuation of Box I Reason 2:
Claim 12 reites the limitation R40a. There is no antecedent basis for this limitation in the claim. Claim 15 is dependent upon an unspecified claim. The metes and bounds of claim 15 could not therefore be determined. Claims 16 and 17 depend upon claim 15.

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
search terms: structure, discodermolide, wittig